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(21) International Application Number: PCT/US99/12272 (22) International Filing Date: 2 June 1999 (02.06.99) (30) Priority Data: 60/094,705 30 July 1998 (30.07.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): O'BRIEN, Patrick, Michael [US/US]; 5501 Green Road, Stockbridge, MI 49285 (US). PICARD, Joseph, Armand [US/US]; 44809 Saltz Road, Canton, MI 48187 (US). SLISKOVIC, Drago, Robert [GB/US]; 3679 Hedgerow Drive, Saline, MI 48176 (US). (74) Agents: RYAN, Andrea, M.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: TRICYCLIC HETEROAROMATICS AND THEIR DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES (57) Abstract <p>Tricyclic heteroaromatic compounds and derivatives are described as well as methods for the preparation and pharmaceutical compositions of same, which are useful as inhibitors of matrix metalloproteinases, particularly gelatinase A, collagenase-3, and stromelysin-1 and for the treatment of multiple sclerosis, atherosclerotic plaque rupture, aortic aneurysm, heart failure, left ventricular dilation, restenosis, periodontal disease, corneal ulceration, treatment of burns, decubital ulcers, wound healing, cancer, inflammation, pain, arthritis, osteoporosis, renal disease, or other autoimmune or inflammatory disorders dependent upon tissue invasion by leukocytes or other activated migrating cells, acute and chronic neurodegenerative disorders including stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy.</p>		

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TRICYCLIC HETEROAROMATICS AND THEIR DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES

BACKGROUND OF THE INVENTION

The present invention relates to novel tricyclic heteroaromatic compounds and their derivatives useful as pharmaceutical agents, to methods for their
5 production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel compounds of the present invention are inhibitors of matrix metalloproteinases, e.g., gelatinase A (MMP-2), collagenase-3 (MMP-13), and
10 stromelysin-1 (MMP-3). More particularly, the novel compounds of the present invention are useful in the treatment of atherosclerotic plaque rupture, aortic aneurism, heart failure, left ventricular dilation, restenosis, periodontal disease, corneal ulceration, treatment of burns, decubital ulcers, wound repair, cancer, inflammation, pain, arthritis, osteoporosis, multiple sclerosis, renal disease, and
15 other autoimmune or inflammatory disorders dependent on the tissue invasion of leukocytes or other activated migrating cells. Additionally, the compounds of the present invention are useful in the treatment of acute and chronic neurodegenerative disorders including stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy,
20 AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy.

Gelatinase A and stromelysin-1 are members of the matrix metalloproteinase (MMP) family (Woessner J.F., *FASEB J.*, 1991;5:2145-2154). Other members include fibroblast collagenase, neutrophil collagenase,
25 gelatinase B (92 kDa gelatinase), stromelysin-2, stromelysin-3, matrilysin, collagenase 3 (Freije J.M., Diez-Itza I., Balbin M., Sanchez L.M., Blasco R., Tolivia J., and Lopez-Otin C., *J. Biol. Chem.*, 1994;269:16766-16773), and the newly discovered membrane-associated matrix metalloproteinases (Sato H., Takino T., Okada Y., Cao J., Shinagawa A., Yamamoto E., and Seiki M., *Nature*,
30 1994;370:61-65).

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The catalytic zinc in matrix metalloproteinases is a focal point for inhibitor design. The modification of substrates by introducing chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and the natural endogenous inhibitors of MMPs (TIMPs) have been used successfully to treat animal models of cancer and inflammation.

The ability of the matrix metalloproteinases to degrade various components of connective tissue makes them potential targets for controlling pathological processes. For example, the rupture of an atherosclerotic plaque is the most common event initiating coronary thrombosis. Destabilization and degradation of the extracellular matrix surrounding these plaques by MMPs has been proposed as a cause of plaque fissuring. The shoulders and regions of foam cell accumulation in human atherosclerotic plaques show locally increased expression of gelatinase B, stromelysin-1, and interstitial collagenase. In situ zymography of this tissue revealed increased gelatinolytic and caseinolytic activity (Galis Z.S., Sukhova G.K., Lark M.W., and Libby P., "Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques," *J. Clin. Invest.*, 1994;94:2494-2503). In addition, high levels of stromelysin RNA message have been found to be localized to individual cells in atherosclerotic plaques removed from heart transplant patients at the time of surgery (Henney A.M., Wakeley P.R., Davies M.J., Foster K., Hembry R., Murphy G., and Humphries S., "Localization of stromelysin gene expression in atherosclerotic plaques by in situ hybridization," *Proc. Nat'l. Acad. Sci.*, 1991;88:8154-8158).

Inhibitors of matrix metalloproteinases will have utility in treating degenerative aortic disease associated with thinning of the medial aortic wall. Increased levels of the proteolytic activities of MMPs have been identified in patients with aortic aneurisms and aortic stenosis (Vine N. and Powell J.T., "Metalloproteinases in degenerative aortic diseases," *Clin. Sci.*, 1991;81:233-239).

Heart failure arises from a number of diverse etiologies, but a common characteristic is cardiac dilation, which has been identified as an independent risk factor for mortality (Lee T.H., Hamilton M.A., Stevenson L.W., Moriguchi J.D.,

Fonarow G.C., Child J.S., Laks H., and Walden J.A., "Impact of left ventricular size on the survival in advanced heart failure," *Am. J. Cardiol.*, 1993;72:672-676). This remodeling of the failing heart appears to involve the breakdown of extracellular matrix. Matrix metalloproteinases are increased in patients with both

5 idiopathic and ischemic heart failure (Reddy H.K., Tyagi S.C., Tjaha I.E., Voelker D.J., Campbell S.E., and Weber K.T., "Activated myocardial collagenase in idiopathic dilated cardiomyopathy," *Clin. Res.*, 1993;41:660A; Tyagi S.C., Reddy H.K., Voelker D., Tjara I.E., and Weber K.T., "Myocardial collagenase in failing human heart," *Clin. Res.*, 1993;41:681A). Animal models of heart failure

10 have shown that the induction of gelatinase is important in cardiac dilation (Armstrong P.W., Moe G.W., Howard R.J., Grima E.A., and Cruz T.F., "Structural remodeling in heart failure: gelatinase induction," *Can. J. Cardiol.*, 1994;10:214-220), and cardiac dilation precedes profound deficits in cardiac function (Sabbah H.N., Kono T., Stein P.D., Mancini G.B., and Goldstein S.,

15 "Left ventricular shape changes during the course of evolving heart failure," *Am. J. Physiol.*, 1992;263:H266-270).

Neointimal proliferation, leading to restenosis, frequently develops after coronary angioplasty. The migration of vascular smooth muscle cells (VSMCs) from the tunica media to the neointima is a key event in the development and

20 progression of many vascular diseases and a highly predictable consequence of mechanical injury to the blood vessel (Bendeck M.P., Zempo N., Clowes A.W., Galaray R.E., and Reidy M., "Smooth muscle cell migration and matrix metalloproteinase expression after arterial injury in the rat," *Circulation Research*, 1994;75:539-545). Northern blotting and zymographic analyses indicated that

25 gelatinase A was the principal MMP expressed and excreted by these cells. Further, antisera capable of selectively neutralizing gelatinase A activity also inhibited VSMC migration across basement membrane barrier. After injury to the vessel, gelatinase A activity increased more than 20-fold as VSMCs underwent the transition from a quiescent state to a proliferating, motile phenotype (Pauly R.R.,

30 Passaniti A., Bilato C., Monticone R., Cheng L., Papadopoulos N., Gluzband Y.A., Smith L., Weinstein C., Lakatta E., and Crow M.T., "Migration of cultured vascular smooth muscle cells through a basement membrane barrier

requires type IV collagenase activity and is inhibited by cellular differentiation," *Circulation Research*, 1994;75:41-54).

Collagenase and stromelysin activities have been demonstrated in fibroblasts isolated from inflamed gingiva (Uitto V.J., Applegren R., and Robinson P.J., "Collagenase and neutral metalloproteinase activity in extracts from inflamed human gingiva," *J. Periodontal Res.*, 1981;16:417-424), and enzyme levels have been correlated to the severity of gum disease (Overall C.M., Wiebkin O.W., and Thonard J.C., "Demonstrations of tissue collagenase activity in vivo and its relationship to inflammation severity in human gingiva," *J. Periodontal Res.*, 1987;22:81-88). Proteolytic degradation of extracellular matrix has been observed in corneal ulceration following alkali burns (Brown S.I., Weller C.A., and Wasserman H.E., "Collagenolytic activity of alkali burned corneas," *Arch. Ophthalmol.*, 1969;81:370-373). Thiol-containing peptides inhibit the collagenase isolated from alkali-burned rabbit corneas (Burns F.R., Stack M.S., Gray R.D., and Paterson C.A., *Invest. Ophthalmol.*, 1989;30:1569-1575).

Stromelysin is produced by basal keratinocytes in a variety of chronic ulcers (Saarialho-Kere U.K., Ulpu K., Pentland A.P., Birkedal-Hansen H., Parks W.O., and Welgus H.G., "Distinct Populations of Basal Keratinocytes Express Stromelysin-1 and Stromelysin-2 in Chronic Wounds," *J. Clin. Invest.*, 1994;94:79-88).

Stromelysin-1 mRNA and protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of the proliferating epidermis. Stromelysin-1 may thus prevent the epidermis from healing.

Davies et al., (*Cancer Res.*, 1993;53:2087-2091) reported that a peptide hydroxamate, BB-94, decreased the tumor burden and prolonged the survival of mice bearing human ovarian carcinoma xenografts. A peptide of the conserved MMP propeptide sequence was a weak inhibitor of gelatinase A and inhibited human tumor cell invasion through a layer of reconstituted basement membrane (Melchiori A., Albili A., Ray J.M., and Stetler-Stevenson W.G., *Cancer Res.*, 1992;52:2353-2356). The natural tissue inhibitor of metalloproteinase-2 (TIMP-2)

also showed blockage of tumor cell invasion in in vitro models (DeClerck Y.A., Perez N., Shimada H., Boone T.C., Langley K.E., and Taylor S.M., *Cancer Res.*, 1992;52:701-708). Studies of human cancers have shown that gelatinase A is activated on the invasive tumor cell surface (Strongin A.Y., Marmer B.L., Grant G.A., and Goldberg G.I., *J. Biol. Chem.*, 1993;268:14033-14039) and is retained there through interaction with a receptor-like molecule (Monsky W.L., Kelly T., Lin C.-Y., Yeh Y., Stetler-Stevenson W.G., Mueller S.C., and Chen W.-T., *Cancer Res.*, 1993;53:3159-3164).

Inhibitors of MMPs have shown activity in models of tumor angiogenesis (Taraboletti G., Garofalo A., Belotti D., Drudis T., Borsotti P., Scanziani E., Brown P.D., and Giavazzi R., *Journal of the National Cancer Institute*, 1995;87:293 and Benelli R., Adatia R., Ensoli B., Stetler-Stevenson W.G., Santi L., and Albini A., *Oncology Research*, 1994;6:251-257).

Several investigators have demonstrated consistent elevation of stromelysin and collagenase in synovial fluids from osteo- and rheumatoid arthritis patients as compared to controls (Walakovits L.A., Moore V.L., Bhardwaj N., Gallick G.S., and Lark M.W., "Detection of stromelysin and collagenase in synovial fluid from patients with rheumatoid arthritis and post-traumatic knee injury," *Arthritis Rheum.*, 1992;35:35-42; Zafarullah M., Pelletier J.P., Cloutier J.M., and Marcel-Pelletier J., "Elevated metalloproteinases and tissue inhibitor of metalloproteinase mRNA in human osteoarthritic synovia," *J. Rheumatol.*, 1993;20:693-697). TIMP-1 and TIMP-2 prevented the formation of collagen fragments, but not proteoglycan fragments in both the bovine nasal and pig articular cartilage models for arthritis, while a synthetic peptide hydroxamate could prevent the formation of both fragments (Andrews H.J., Plumptre T.A., Harper G.P., and Cawston T.E., *Agents Actions*, 1992;37:147-154; Ellis A.J., Curry V.A., Powell E.K., and Cawston T.E., *Biochem. Biophys. Res. Commun.*, 1994;201:94-101).

Gijbels et al., (*J. Clin. Invest.*, 1994;94:2177-2182) recently described a peptide hydroxamate, GM6001, that suppressed the development or reversed the clinical expression of experimental autoimmune encephalomyelitis (EAE) in a

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dose dependent manner, suggesting the use of MMP inhibitors in the treatment of autoimmune inflammatory disorders such as multiple sclerosis.

A recent study by Madri has elucidated the role of gelatinase A in the extravasation of T-cells from the blood stream during inflammation
5 (Ramanic A.M., and Madri J.A., "The Induction of 72-kDa Gelatinase in T Cells upon Adhesion to Endothelial Cells is VCAM-1 Dependent," *J. Cell Biology*, 1994;125:1165-1178). This transmigration past the endothelial cell layer is coordinated with the induction of gelatinase A and is mediated by binding to the vascular cell adhesion molecule-1 (VCAM-1). Once the barrier is compromised,
10 edema and inflammation are produced in the CNS. Also, leukocytic migration across the blood-brain barrier is known to be associated with the inflammatory response in EAE. Inhibition of the metalloproteinase gelatinase A would block the degradation of extracellular matrix by activated T-cells that is necessary for CNS penetration.

15 These studies provide the basis for the expectation that an effective inhibitor of gelatinase A and/or stromelysin-1 would have value in the treatment of diseases involving disruption of extracellular matrix resulting in inflammation due to lymphocytic infiltration, inappropriate migration of metastatic or activated cells, or loss of structural integrity necessary for organ function.

20 Neuroinflammatory mechanisms are implicated in a broad range of acute and chronic neurodegenerative disorders, including stroke, head trauma, multiple sclerosis, and Alzheimer's disease, to name a few (McGeer E.G. and McGeer P.L., "Neurodegeneration and the immune system". In: Calne D.B., ed. Neurodegenerative Diseases, W.B. Saunders, 1994:277-300). Other disorders that
25 may involve neuroinflammatory mechanisms include amyotrophic lateral sclerosis (Leigh P.N., "Pathogenic mechanisms in amyotrophic lateral sclerosis and other motor neuron disorders". In: Calne D.B., ed., Neurodegenerative Diseases, W.B. Saunders, 1994:473-88), cerebral amyloid angiopathy (Mandybur T.I. and Balko G., "Cerebral amyloid angiopathy with granulomatous angiitis ameliorated
30 by steroid-cytoxan treatment," *Clin. Neuropharm.*, 1992;15:241-7), AIDS (Gendelman H.E. and Tardieu M., "Macrophages/microglia and the pathophysiology of CNS injuries in AIDS," *J. Leukocyte Biol.*, 1994;56:387-8),

Parkinson's disease, Huntington's disease, prion diseases, and certain disorders involving the peripheral nervous system, such as myasthenia gravis and Duchenne's muscular dystrophy. Neuroinflammation, which occurs in response to brain injury or autoimmune disorders, has been shown to cause destruction of healthy tissue (Martin R., MacFarland H.F., and McFarlin D.E., "Immunological aspects of demyelinating diseases," *Annu Rev. Immunol.*, 1992;10:153-87; Clark R.K., Lee E.V., Fish C.J., et al., "Development of tissue damage, inflammation and resolution following stroke: an immunohistochemical and quantitative planimetric study," *Brain Res. Bull.*, 1993;31:565-72; Giulian D. and Vaca K., "Inflammatory glia mediate delayed neuronal damage after ischemia in the central nervous system," *Stroke*, 1993;24(Suppl 12):184-90; Patterson P.H., "Cytokines in Alzheimer's disease and multiple sclerosis," *Cur. Opinion Neurobiol.*, 1995;5:642-6; McGeer P.L., Rogers J., and McGeer E.G., "Neuroimmune mechanisms in Alzheimer disease pathogenesis," *Alzheimer Dis. Assoc. Disorders*, 1994;8:149-58; Martin R. and McFarland H.F., "Immunological aspects of experimental allergic encephalomyelitis and multiple sclerosis," *Crit. Rev. Clin. Lab. Sci.*, 1995;32:121-82; Rogers J., Webster S., Lue L.F., et al., "Inflammation and Alzheimer's disease pathogenesis". In: *Neurobiology of Aging*, 1996;17:681-686; Rothwell N.J. and Relton J.K., "Involvement of cytokines in acute neurodegeneration in the CNS," *Neurosci. Biobehav. Rev.*, 1993;17:217-27). The pathological profiles and clinical courses of these disorders differ widely, but they all have in common the participation of immune/inflammatory elements in the disease process. In particular, many neurodegenerative disorders are characterized by large numbers of reactive microglia in postmortem brain samples, indicative of an active inflammatory process (McGeer E.G. and McGeer P.L., supra., 1994).

Increasing attention is being directed toward inflammatory mechanisms in Alzheimer's disease. Several lines of evidence support the involvement of neuroinflammation in Alzheimer's disease: 1) There is a significant increase in inflammatory markers in the Alzheimer brain, including acute phase reactants, cytokines, complement proteins, and MHC molecules (McGeer et al., supra., 1994; Rogers et al., supra.); 2) There is evidence that β -amyloid induces

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neurodegenerative changes primarily through interactions with inflammatory molecules, and that inflammation alone is sufficient to induce neurodegeneration (Rogers et al., supra); and 3) Growing epidemiological data indicate that anti-inflammatory therapy can delay the onset and slow the progression of Alzheimer's disease (McGeer P.L. and Rogers J., "Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease," *Neurology*, 1992;42:447-9; Canadian Study of Health and Aging, "Risk factors for Alzheimer's disease in Canada," *Neurology*, 1994;44:2073-80; Lucca U., Tettamanti M., Forloni G., and Spagnoli A., "Nonsteroidal antiinflammatory drug use in Alzheimer's disease," *Biol. Psychiatry*, 1994;36:854-66; Hampel H. and Müller N., "Inflammatory and immunological mechanisms in Alzheimer's disease," *DN&P*, 1995;8:599-608; Breitner J.C.S., Gau B.A., Welsh K.A., et al., "Inverse association of anti-inflammatory treatments and Alzheimer's disease: Initial results of a co-twin control study," *Neurology*, 1994;44:227-32; Breitner J.C.S., Welsh K.A., Helms M.J., et al., "Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs," *Neurobiol. Aging*, 1995;16:523-30; Andersen K., Launer L.J., Ott A., Hoes A.W., Breteler M.M.B., and Hofman A., "Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study," *Neurology*, 1995;45:1441-5; Rich J.B., Rasmusson D.X., Folstein M.F., et al., "Nonsteroidal anti-inflammatory drugs in Alzheimer's disease," *Neurology*, 1995;45:51-5; Aisen P.S., "Anti-inflammatory therapy for Alzheimer's disease," *Dementia*, 1995;9:173-82; Rogers et al., supra). Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), most commonly for the treatment of rheumatoid arthritis, decreases the probability of developing Alzheimer's disease, and there is reason to believe that other anti-inflammatory agents may also be effective, although direct evidence for the efficacy of such treatments is lacking (Hamper and Müller, supra., 1995). Furthermore, virtually all of the currently available compounds, which include corticosteroids, NSAIDs, antimalarial drugs, and colchicine, have serious drawbacks that make them undesirable in the treatment of chronic disorders. Glucocorticoids, which are in wide clinical use as anti-inflammatory/immunosuppressive drugs, can be directly neurotoxic and also are

toxic to systemic organs at moderate to high doses. NSAIDs have gastrointestinal and renal side effects that obviate long-term use in most people, and few of them cross the blood-brain barrier in significant amounts. The toxic properties of chloroquine compounds and colchicine also are well known. An anti-inflammatory drug that is well-tolerated by patients and that crosses the blood-brain barrier has significant advantages for the treatment of acute and chronic degenerative diseases of the central nervous system.

Normal kidney function is dependent on the maintenance of tissues constructed from differentiated and highly specialized renal cells which are in a dynamic balance with their surrounding extracellular matrix (ECM) components (Davies M. et al., "Proteinases and glomerular matrix turnover," *Kidney Int.*, 1992;41:671-678). Effective glomerular filtration requires that a semi-permeable glomerular basement membrane (GBM) composed of collagens, fibronectin, enactin, laminin and proteoglycans is maintained. A structural equilibrium is achieved by balancing the continued deposition of ECM proteins with their degradation by specific metalloproteinases (MMP). The MMP belong to a supergene family of zinc endopeptidases (Woessner J.F., "Matrix metalloproteinases and their inhibitors in connective tissue remodelling," *FASEB J.*, 1991;5:2145-2154). These proteins are first secreted as proenzymes and are subsequently activated in the extracellular space. These proteinases are in turn subject to counter balancing regulation of their activity by naturally occurring inhibitors referred to as TIMPs (tissue inhibitors of metalloproteinases).

Deficiency or defects in any component of the filtration barrier may have catastrophic consequences for longer term renal function. For example, in hereditary nephritis of Alport's type, associated with mutations in genes encoding ECM proteins, defects in collagen assembly lead to progressive renal failure associated with splitting of the GBM and eventual glomerular and interstitial fibrosis. By contrast in inflammatory renal diseases such as glomerulonephritis, cellular proliferation of components of the glomerulus often precede obvious ultrastructural alteration of the ECM matrix. Cytokines and growth factors implicated in proliferative glomerulonephritis such as interleukin-1, tumor necrosis factor, and transforming growth factor beta can upregulate

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metalloproteinase expression in renal mesangial cells (Martin J. et al.,
"Enhancement of glomerular mesangial cell neutral proteinase secretion by
macrophages: role of interleukin 1," *J. Immunol.*, 1986;137:525-529; Marti H.P.
et al., "Homology cloning of rat 72 kDa type IV collagenase: Cytokine and
5 second-messenger inducibility in mesangial cells," *Biochem. J.*,
1993;291:441-446; Marti H.P. et al., "Transforming growth factor- β stimulates
glomerular mesangial cell synthesis of the 72 kDa type IV collagenase," *Am. J.*
Pathol., 1994;144:82-94). These metalloproteinases are believed to be intimately
involved in the aberrant tissue remodeling and cell proliferation characteristic of
10 renal diseases, such as, IgA nephropathy which can progress to through a process
of gradual glomerular fibrosis and loss of functional GBM to end-stage renal
disease. Metalloproteinase expression has already been well-characterized in
experimental immune complex-mediated glomerulonephritis such as the anti-
Thy 1.1 rat model (Bagchus W.M., Hoedemaeker P.J., Rozing J., Bakker W.W.,
15 "Glomerulonephritis induced by monoclonal anti-Thy 1.1 antibodies: A sequential
histological and ultrastructural study in the rat," *Lab. Invest.*, 1986;55:680-687;
Lovett D.H., Johnson R.J., Marti H.P., Martin J., Davies M., Couser W.G.,
"Structural characterization of the mesangial cell type IV collagenase and
enhanced expression in a model of immune complex mediated
20 glomerulonephritis," *Am. J. Pathol.*, 1992;141:85-98).

Unfortunately, at present, there are very limited therapeutic strategies for
modifying the course of progressive renal disease. Although many renal diseases
have an inflammatory component, their responses to standard immunosuppressive
regimes are unpredictable and potentially hazardous to individual patients. The
25 secondary consequences of gradual nephron failure such as activation of the renin-
angiotensin system, accompanied by individual nephron glomerular hyperfiltration
and renal hypertension, may be effectively treated with ACE inhibitors or
angiotensin II receptor antagonists; but at best, these compounds can only reduce
the rate of GFR decline.

30 A novel strategy to treat at least some renal diseases has been suggested by
recent observations of MMP behavior. A rat mesangial cell MMP has been cloned
(MMP-2) which is regulated in a tissue specific manner, and in contrast to other

cellular sources such as tumor cell lines, is induced by cytokines (Brown P.D.,
Levy A.T., Margulies I., Liotta L.A., Stetler-Stevenson W.G., "Independent
expression and cellular processing of Mr 72,000 type IV collagenase and
interstitial collagenase in human tumorigenic cell lines," *Cancer Res.*,
5 1990;50:6184-6191; Marti H.P. et al., "Homology cloning of rat 72 kDa type IV
collagenase: Cytokine and second-messenger inducibility in mesangial cells,"
Biochem. J., 1993;291:441-446). While MMP-2 can specifically degrade
surrounding ECM, it also affects the phenotype of adjacent mesangial cells.
Inhibition of MMP-2 by antisense oligonucleotides or transfection techniques can
10 induce a reversion of the proliferative phenotype of cultured mesangial cells to a
quiescent or non-proliferative phenotype mimicking the natural in vitro behavior
of these cells (Kitamura M. et al., "Gene transfer of metalloproteinase transin
induces aberrant behaviour of cultured mesangial cells," *Kidney Int.*,
1994;45:1580-1586; Turck J. et al., "Matrix metalloproteinase 2 (gelatinase A)
15 regulates glomerular mesangial cell proliferation and differentiation," *J. Biol.*
Chem., 1996;271:15074-15083).

Inhibitors of MMP (MMPi) clearly have potential clinical applications in a
host of diseases characterized by disturbance of extracellular matrix-cell
interactions resulting in abnormal tissue remodeling (Vincenti M.P. et al., "Using
20 inhibitors of metalloproteinases to treat arthritis," *Arthritis Rheum.*, 1994;8:1115-
1126; Grams F. et al., "X-ray structures of human neutrophil collagenase
complexed with peptide hydroxamate and peptide thiol inhibitors. Implications for
substrate binding and rational drug design," *Eur. J. Biochem.*, 1995;228:830-841).

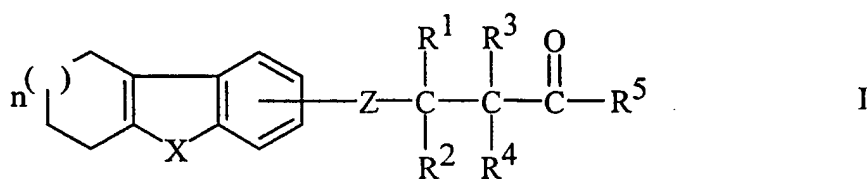
We have identified a series of tricyclic heteroaromatic compounds and
25 their derivatives that are inhibitors of matrix metalloproteinases, particularly
collagenase-3, stromelysin-1 and gelatinase A, and thus useful as agents for the
treatment of multiple sclerosis, atherosclerotic plaque rupture, restenosis, aortic
aneurism, heart failure, left ventricular dilation, periodontal disease, corneal
ulceration, treatment of burns, decubital ulcers, wound repair, cancer,
30 inflammation, pain, arthritis, osteoporosis, renal disease, or other autoimmune or
inflammatory diseases dependent upon tissue invasion by leukocytes or other
activated migrating cells, acute and chronic neurodegenerative disorders including

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stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's diseases, prion diseases, myasthenic gravis, and Duchenne's muscular dystrophy.

SUMMARY OF THE INVENTION

5 Accordingly, a first aspect of the present invention is a compound of Formula I



wherein n is zero or an integer of 1 or 2;

X is -O-,

10 -S(O)_p- wherein p is zero or an integer of 1 or 2,

-N- wherein R⁶ is hydrogen, alkyl, acyl, or benzyl,

|
R⁶

-CH₂-, or

15 -C-;

||
O

O
||

20 Z is -C-,

OH
|

-CH-,

25 S
||
-C-,

CF₂,

CHF,

-CH₂-,

N-R⁷

||

5 -C- wherein R⁷ is OR⁸ wherein R⁸ is hydrogen,

alkyl,

-(CH₂)_m-aryl wherein m is zero or an integer of 1 to 6,

-(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above or

10 N-R⁹ wherein R⁹ and R^{9a} are either the same or different

|
R^{9a}

and are hydrogen,

alkyl,

15 aryl,

arylalkyl,

heteroaryl, or

cycloalkyl;

R¹, R², R³, and R⁴ are either the same or different and are

20 hydrogen,

fluorine,

alkyl,

alkenyl,

alkynyl,

25 arylalkenyl,

heteroarylalkenyl,

arylalkynyl,

heteroarylalkynyl,

-(CH₂)_m-aryl wherein m is as defined above,

30 -(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above,

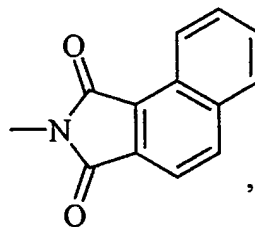
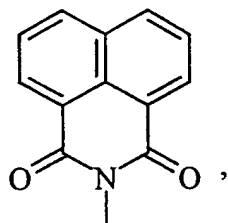
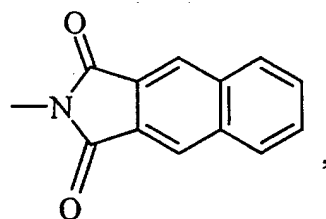
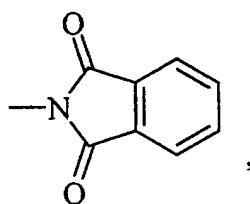
-14-

$-(CH_2)_q-X^a-(CH_2)_{q^1}$ -alkyl wherein X^a is O, S, SO, SO₂, or NH, and q and q^1 are each zero or an integer of 1 to 6, and the sum of $q + q^1$ is not greater than six,

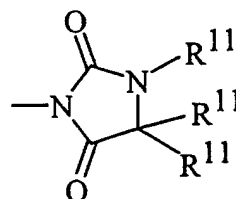
$-(CH_2)_q-X^a-(CH_2)_{q^1}$ -aryl wherein X^a , q , and q^1 are as defined above,

5 $-(CH_2)_q-X^a-(CH_2)_{q^1}$ -heteroaryl wherein X^a , q , and q^1 are as defined above, or

$-(CH_2)_m-R^{10}$ wherein R^{10} is

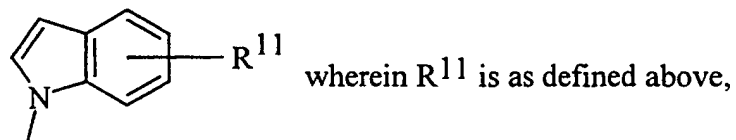
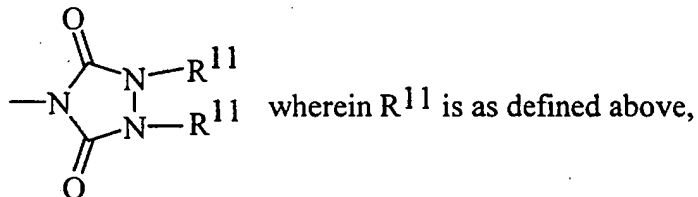
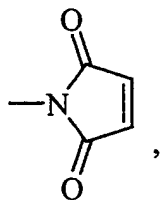
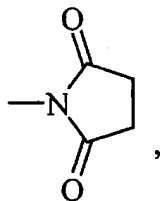
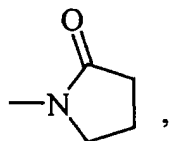


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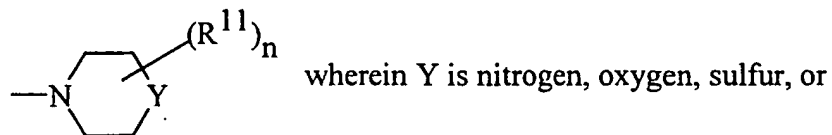


wherein R^{11} is hydrogen, alkyl, aryl, arylalkyl,

heteroaryl, or cycloalkyl,



5



CH₂ and R¹¹ and n are as defined above and m is as defined above,

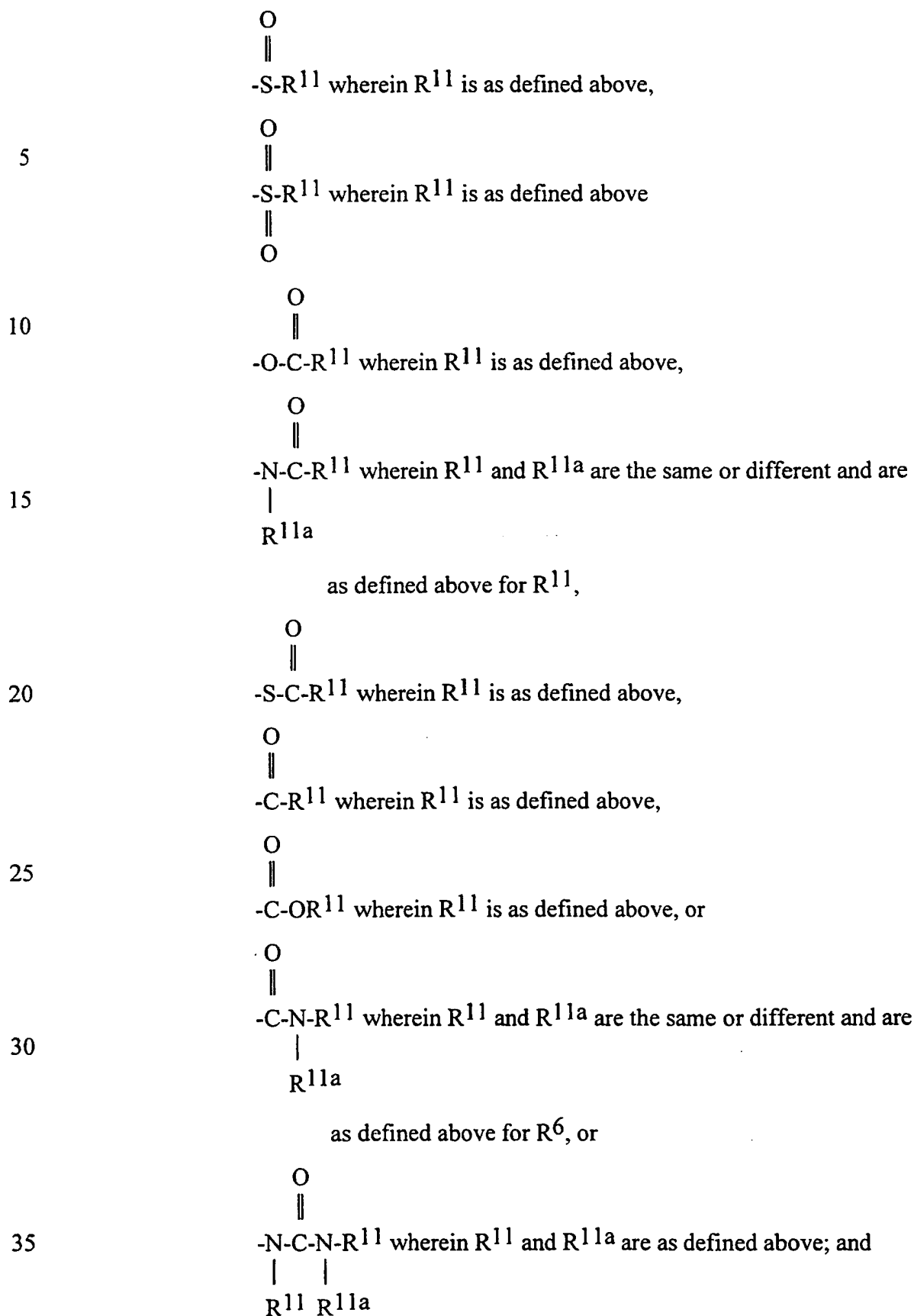
OR¹¹ wherein R¹¹ is as defined above,

10

-N-R¹¹ wherein R¹¹ and R^{11a} are the same or different and are as defined above for R¹¹,

-SR¹¹ wherein R¹¹ is as defined above,

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R⁵ is -OR¹² wherein R¹² is hydrogen,

alkyl, or

benzyl,

-NH-OR¹² wherein R¹² is as defined above, or

-SH;

5



with the proviso that when n is 1, X is -O-, Z is -C-, and R⁵ is OR¹² wherein R¹² is as defined above, then at least one of R¹, R², R³, and R⁴ is not hydrogen; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

10

As matrix metalloproteinase inhibitors, the compounds of Formula I are useful as agents for the treatment of multiple sclerosis. They are also useful as agents for the treatment of atherosclerotic plaque rupture, aortic aneurism, heart failure, left ventricular dilation, restenosis, periodontal disease, corneal ulceration, treatment of burns, decubital ulcers, wound repair, cancer metastasis, tumor

15 angiogenesis, inflammation, pain, arthritis, osteoporosis, renal disease, and other autoimmune or inflammatory disorders dependent upon tissue invasion by leukocytes or other activated migrating cells, acute and chronic neurodegenerative disorders including stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's

20 disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy.

20

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above. Finally, the present

25 invention is directed to methods for production of compounds of Formula I.

25

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec-butyl, isobutyl, tert-butyl,

30 *n*-pentyl, *n*-hexyl, and the like.

30

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The term "alkenyl" means a straight or branched unsaturated hydrocarbon radical having from 2 to 10 carbon atoms and includes, for example, ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, 1-octenyl, 1-nonenyl, 1-decenyl, and the like.

The term "alkynyl" means a straight or branched triple bonded unsaturated hydrocarbon radical having from 2 to 10 carbon atoms and includes, for example, ethynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 3-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 3-heptylnyl, 1-octynyl, 2-octynyl, 1-nonylnyl, 2-nonylnyl, 3-nonylnyl, 4-nonylnyl, 1-decynyl, 2-decynyl, and the like.

"Alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "alkyl".

The term "cycloalkyl" means a saturated hydrocarbon ring having 3 to 7 carbon atoms optionally containing an oxygen or sulfur atom and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "aryl" means an aromatic radical which is a phenyl group, a phenyl group substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, halogen, trifluoromethyl, amino, alkylamino as defined above for alkyl, dialkylamino as defined above for alkyl, nitro, cyano, carboxy, guanidino, amidino, SO₃H, CHO,

C-alkyl as defined above for alkyl, -C(=O)-NH_2 , -C(=O)-NH-alkyl , NH-C(=O)-alkyl ,

as defined above for alkyl, -C(=O)-N(alkyl)_2 as defined above for alkyl,

$\text{-(CH}_2\text{)}_{n^2}\text{-NH}_2$ wherein n^2 is an integer of 1 to 5, $\text{-(CH}_2\text{)}_{n^2}\text{-NH-alkyl}$ as defined above for alkyl and n^2 , $\text{-(CH}_2\text{)}_{n^2}\text{-N(alkyl)}_2$ as defined above for alkyl and n^2 ,

$\text{-(CH}_2\text{)}_{n^2}\text{-NH-C(=O)-alkyl}$ as defined above for alkyl, and n^2 and $\text{-(CH}_2\text{)}_{n^2}\text{-N-C(=O)-alkyl}$

as defined above for alkyl and n^2 .

The term "arylalkyl" means an aromatic radical attached to an alkyl radical wherein aryl and alkyl are as defined above for example benzyl, phenylethyl, 3-phenylpropyl, (4-chlorophenyl)methyl, and the like.

5 The term "arylalkenyl" means an aromatic radical attached to an alkenyl radical wherein aryl and alkyl are as defined above.

The term "arylalkynyl" means an aromatic radical attached to an alkynyl radical wherein aryl and alkynyl are as defined above.

10 The term "heteroaryl" means a 5- and 6-membered heteroaromatic radical containing 1 to 3 heteroatoms selected from N, O, and S and includes, for example, a heteroaromatic radical which is 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 3-, or 4-pyridinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-5-yl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, or 2- or 5-thiadiazolyl optionally substituted by a substituent selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, halogen, trifluoromethyl, amino, alkylamino as defined above for alkyl, dialkylamino as defined above for alkyl, nitro, cyano, carboxy, guanidino, amidino, SO_3H , CHO,

20 $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-alkyl} \end{array}$ as defined above for alkyl, $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C-NH}_2 \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C-NH-alkyl} \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{NH-C-alkyl} \end{array}$,

25 $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C-N(alkyl)}_2 \end{array}$ as defined above for alkyl,

$-(\text{CH}_2)_{n^2}\text{-NH}_2$ wherein n^2 is an integer of 1 to 5, $-(\text{CH}_2)_{n^2}\text{-NH-alkyl}$ as defined above for alkyl and n^2 , $-(\text{CH}_2)_{n^2}\text{-N(alkyl)}_2$ as defined above for alkyl and n^2 ,

30 $\begin{array}{c} \text{O} \\ \parallel \\ -(\text{CH}_2)_{n^2}\text{-NH-C-alkyl} \end{array}$ as defined above for alkyl, and n^2 and $\begin{array}{c} \text{O} \\ \parallel \\ -(\text{CH}_2)_{n^2}\text{-N-C-alkyl} \\ | \\ \text{alkyl} \end{array}$

as defined above for alkyl and n^2 .

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The term "heteroarylalkenyl" means a heteroaryl radical attached to an alkenyl radical wherein heteroaryl and alkenyl are as defined above.

The term "heteroarylalkynyl" means a heteroaryl radical attached to an alkynyl radical wherein heteroaryl and alkynyl are as defined above.

5



The term "acyl" means a group of the formula -C-alkyl wherein alkyl is as defined above.

"Halogen" is fluorine, chlorine, bromine, or iodine.

10

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

Some of the compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

15

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma. Sci.*, 1977;66:1).

20
25
30

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt

in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977;66:1).

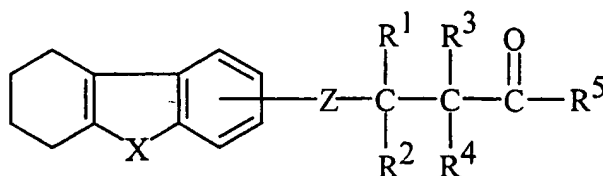
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

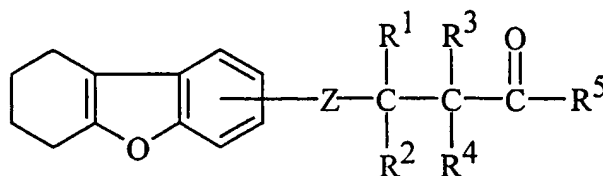
A preferred compound of Formula I is

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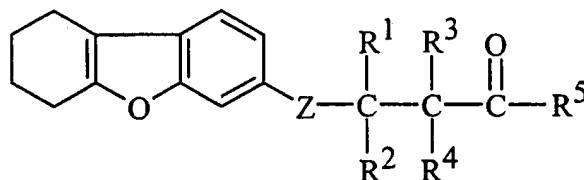
wherein X, Z, R¹, R², R³, R⁴, and R⁵ are as defined above.

Another preferred compound of Formula I is



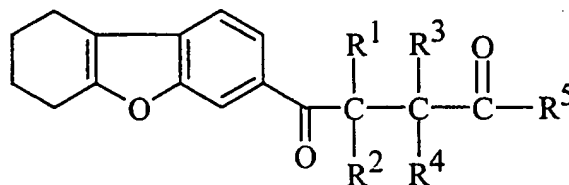
5 wherein Z, R¹, R², R³, R⁴, and R⁵ are as defined above.

Another preferred compound of Formula I is



wherein Z, R¹, R², R³, R⁴, and R⁵ are as defined above.

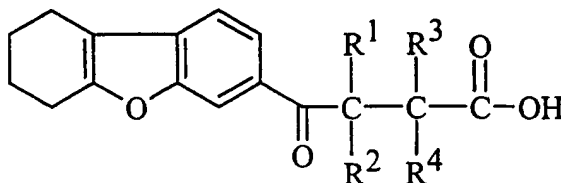
Another preferred compound of Formula I is



10

wherein R¹, R², R³, R⁴, and R⁵ are as defined above.

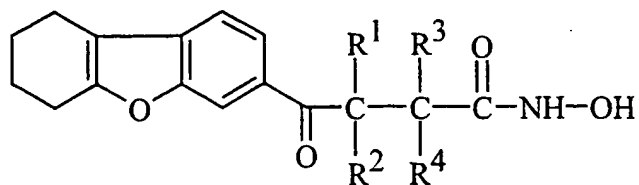
A more preferred compound of Formula I is



wherein R¹, R², R³, and R⁴ are as defined above.

15

A most preferred compound of Formula I is



Particularly valuable in this embodiment of the invention is a compound selected from the group consisting of:

- 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- 5 N-Hydroxy-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyramide;
- N-Hydroxy-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyramide;
- 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-butyric acid;
- 10 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-butyric acid;
- 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;
- 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-
- 15 hexanoic acid;
- 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;
- 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;
- 20 (S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-
- 25 phenyl-hexanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;

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- (S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- 5 (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;
- (S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-
- 10 (6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;
- (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 15 (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-
- 20 trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 25 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-2-phenethyl-butyl butyric acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-
- 30 phenyl-heptanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-phenyl-octanoic acid;

5 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-phenyl-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-phenyl-hexanoic acid;

10 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-phenyl-pentanoic acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-phenethyl-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyric acid;

15 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

20 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

25 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

30 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

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(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-oxo-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(1H-indol-3-ylmethyl)-4-oxo-butyric acid;

5 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-oxo-butyric acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

10 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-hydroxyimino-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

15 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1H-indol-3-yl)-ethyl]-4-oxo-butyric acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

20 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

25 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

30 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-(1H-indol-3-ylmethyl)-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-[2-(1H-indol-3-yl)-ethyl]-butyric acid;

- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1H-indol-3-yl)-octanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;
- 5 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxy-butyric acid;
- 4-Hydroxy-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-
- 10 pentanoic acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;
- 15 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;
- 4-Hydroxy-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 4-Hydroxy-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-
- 20 2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxy-butyric acid;
- 25 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-
- 30 hexanoic acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;

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(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;

4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

5 (S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;

10 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;

15 (S) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(S) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

20 (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

25 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

(S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

30 (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;

- (S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 5 (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;
- 4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-butyric acid;
- 4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-butyric acid;
- 10 4-Oxo-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;
- 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;
- (S) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;
- 15 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- 20 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;
- (S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;
- 25 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- 30 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

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- 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-butyric acid;
4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-butyric acid;
(S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-
2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
5 (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-
trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-
trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
(S) 4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-
10 phenethyl-butyl-butiric acid;
(S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-
ethyl]-5-phenyl-pentanoic acid;
(S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-
ethyl]-6-phenyl-hexanoic acid;
15 (S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-
ethyl]-7-phenyl-heptanoic acid;
(S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-
ethyl]-8-phenyl-octanoic acid;
(S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-
20 trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
(S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-
(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-
ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
25 (S) 4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-2-phenethyl-
butyric acid;
(S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-5-
phenyl-pentanoic acid;
(S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-6-
30 phenyl-hexanoic acid;
(S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-7-
phenyl-heptanoic acid;

(S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

5 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;

10 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

15 (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

20 (R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

25 (R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

30 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

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(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

5 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-2-phenethyl-butyrlic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;

10 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;

15 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-phenyl-octanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-phenyl-heptanoic acid;

20 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-phenyl-pentanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-phenethyl-butyrlic acid;

25 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyrlic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

30 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

5 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

10 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-oxo-butyric acid;

15 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(1H-indol-3-ylmethyl)-4-oxo-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-oxo-butyric acid;

20 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-hydroxyimino-butyric acid;

25 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1H-indol-3-yl)-ethyl]-4-oxo-butyric acid;

30 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

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(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

5 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

10 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-(1H-indol-3-ylmethyl)-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-[2-(1H-indol-3-yl)-ethyl]-butyric acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

15 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(R) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

20 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;

25 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

30 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;

5 (R) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

10 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

15 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

20 (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

(R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;

(R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

25 (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

(R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;

30 (R) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

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(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

5 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

10 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

15 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

20 (R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-phenethyl-butyric acid;

25 (R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-6-phenyl-hexanoic acid;

30 (R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-7-phenyl-heptanoic acid;

(R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

5 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-2-phenethyl-butyric acid;

10 (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid; and

15 (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;

and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

20 The compounds of Formula I are valuable inhibitors of a number of different matrix metalloproteinases. It has been shown previously that inhibitors of matrix metalloproteinases have efficacy in models of disease states like arthritis and metastasis that depend on modification of the extracellular matrix.

25 In vitro experiments were carried out which demonstrate the efficacy of compounds of Formula I as potent and specific inhibitors of a variety of matrix metalloproteinases. Experiments were carried out with the full-length and catalytic domains of the proteinases. Table 1 shows the activity of Examples 1-2 versus MMP-1FL (collagenase-1 full length enzyme), MMP-2CD (gelatinase A catalytic domain), MMP-2FL (gelatinase A full length enzyme), MMP-3CD (stromelysin-1 catalytic domain), MMP-7FL (matrilysin full length enzyme), MMP-9-FL (gelatinase B full length enzyme), MMP-13CD (collagenase-3 catalytic domain),
30 and MMP-14CD (membrane-type MMP-1). IC₅₀ values were determined using a thiopeptolide substrate, Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt (Ye Q.-Z., Johnson L.L., Hupe D.J., and Baragi V., "Purification and Characterization of the

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Human Stromelysin Catalytic Domain Expressed in *Escherichia coli*,”
Biochemistry, 1992;31:11231-11235; Ye Q.-Z., Johnson L.L., Yu A.E., and Hupe
D., “Reconstructed 19 kDa catalytic domain of gelatinase A is an active
proteinase,” *Biochemistry*, 1995;34:4702-4708.) MMP-13CD was expressed from
5 a synthetic gene and purified from *Escherichia coli* cell culture according to a
previously described method (Ye Q.-Z., Johnson L.L., and Baragi V., “Gene
synthesis and expression in *E. coli* for PUMP, a human matrix metalloproteinase,”
Biochemical and Biophysical Research Communications, 1992;186:143-149).

TABLE 1. Biological Activity of Compounds of Formula I

Example	IC ₅₀ (μM)							
	MMP-1FL	MMP-2CD	MMP-2FL	MMP-3CD	MMP-7FL	MMP-9FL	MMP-13CD	MMP-14CD
1	100	0.01835	0.0595	0.1145	100	32	1.206667	0.24
2	67	0.096	0.445	0.13	84	100	9.7	0.82
3	31	0.0585	0.945	0.315	86	14	1.42	2

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The following list contains abbreviations and acronyms used within the schemes and text:

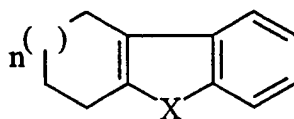
GBM	Glomerular basement membrane
ECM	Extracellular matrix
CNS	Central nervous system
CH ₂ Cl ₂	Dichloromethane
EAE	Experimental autoimmune encephalomyelitis
MMP	Matrix metalloproteinase
TIMPs	Tissue inhibitors of matrix metalloproteinases
VSMC	Vascular smooth muscle cell
TFA	Trifluoroacetic acid
IC ₅₀	Concentration of compound required to inhibit 50% of enzyme activity
HCl	Hydrogen chloride
THF	Tetrahydrofuran
Pd	Palladium
Na	Sodium
NaH	Sodium hydride
LiOH	Lithium hydroxide
LiCl	Lithium Chloride
H ₂ O	Water
H ₂	Hydrogen
CDI	1,1'-Carbonyldiimidazole
hν	light
SO ₃ ·DMF	Sulfur trioxide dimethyl formamide
SOCl ₂	Thionyl Chloride
t-Bu	tertiary butyl
BOC	tertiary butoxycarbonyl
LDA	Lithium diisopropylamide
MeOH	Methanol

DMF	Dimethylformamide
p-TsOH(p-TSA)	para-Toluenesulfonic acid
CHCl ₃	Chloroform
CDCl ₃	Deuterated chloroform
E	Entgegen
Z	Zusammen
H ₂ NOBz	O-Benzyl hydroxylamine
TEA, Et ₃ N	Triethylamine
CH ₃ CN	Acetonitrile
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
PPA	Polyphosphoric acid
BaSO ₄	Barium sulfate
DMSO-d ₆	Deuterated dimethylsulfoxide
MgSO ₄	Magnesium sulfate
¹ H-NMR	Proton nuclear magnetic resonance
PPM	Parts per million
MS	Mass spectrum
CI-MS	Chemical ionization mass spectrum
NaNO ₂	Sodium nitrite
KBr	Potassium bromide
N ₂	Nitrogen
AlCl ₃	Aluminum chloride
ZnCl ₂	Zinc chloride
SnCl ₂	Stannous chloride
FeCl ₃	Ferric chloride
ClCH ₂ CH ₂ Cl(DCE)	Dichloroethane
H ₂ S	Hydrogen sulfide
NaOAc	Sodium acetate

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KHMDS	Potassium hexamethyldisilazide
NBS	N-bromosuccinimide
PG	Protecting group
CCl ₄	Carbon tetrachloride
NFSI	N-Fluorobenzenesulfonimide
EtOH	Ethanol
(COCl) ₂	Oxalyl chloride
Et ₃ SiH	Triethylsilane
Lawesson's reagent	[2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]
DAST	Diethylaminosulfur trifluoride
KOH	Potassium hydroxide
NaBH ₄	Sodium borohydride
TMS-Cl	Chlorotrimethylsilane
i-C ₄ H ₉ OCOC	Isobutyl chloroformate

Tricyclic aryl and tricyclic heteroaryl starting materials of formula (3)



(3)

wherein n is zero or an integer of 1 or 2; and

5 X is -O-,

-S(O)_p-wherein p is zero or an integer of 1 or 2,

-N-, wherein R⁶ is hydrogen, alkyl, acyl, or benzyl,

|
R⁶

10 -CH₂-, or

-C-
||
O

are either obtained from commercial sources ($X = N-R^6$ wherein R^6 is as defined above) or prepared using methods known in the art, e.g., Bachelet J.P. and Caubere P., *J. Org. Chem.*, 1982;47:234-238; Ebel F., *Helv. Chim. Acta*, 1929;12:3-16; Vanrysselberghe V. et al., *Ind. Eng. Chem. Res.*, 1996;35:3311-3318; Derouane D. et al., *J. Chem. Soc., Chem. Commun.*, 1995;10:993-994; Miki Y. and Sugimoto Y., *Seikiyu Gakkaishi*, 1994;37:386-394; Miki Y. et al., *Seikiyu Gakkaishi*, 1992;35:332-338; Rankel L.A., *Fuel Sci. Technol. Int.*, 1991;9:1435-1447; Siskin M. et al., *Energy Fuels*, 1990;4:482-488; Sundaram K.M. et al., *Chem. Eng. Commun.*, 1988;71:53-71; Francisco M.A. et al., *J. Org. Chem.*, 1988;53:596-600; Nagai M. et al., *J. Catal.*, 1986;97:52-58; Miyake M. et al., *Bull. Chem. Soc. Japan*, 1979;52:559-563; Ando W. et al., *J. Chem. Soc. Chem. Commun.*, 1975;17:704-705; Fraser P.S. et al., *J. Org. Chem.*, 1974;39:2509-2513; Cagniant P. et al., *Bull. Soc. Chim. Fr.*, 1969;2:607-612; and Cagniant D. et al., *Bull. Soc. Chim. Fr.*, 1969;2:601-606; United States Patents 5,721,185, 5,670,680; International Published Patent Application WO 95/27717; Smith W. et al., *J. Org. Chem.*, 1990;55:5301-5302; Mejer S., *Pol. of Chem.*, 1979;53:2385-2388; Canonne P. et al., *J. Org. Chem.*, 1980;45:1828-1835; Parham W.E., *Synthesis*, 1976;116-117; Japanese Patent Application JP 08191063 A2; Parhan W.E., *J. Org. Chem.*, 1969;34:1899-1904; McClure K.F. et al., *Bioorg. Med. Chem. Lett.*, 1998;8:143-146.

The synthesis of starting materials for a compound of Formula I wherein X is -O- is shown in Scheme 1 (Ebel's method). Thus, a compound of formula (1) wherein n is zero or an integer of 1 or 2 is reacted with phenol in the presence of sodium, or sodium hydride and the like in the presence of a solvent such as benzene, tetrahydrofuran and the like to afford a compound of formula (2). Cyclization of a compound of formula (2) in the presence of an acid such as, for example, polyphosphoric acid, para-toluenesulfonic acid and the like in the presence of a solvent such as benzene and the like affords a compound of formula (3). Ebel's method for the synthesis of 1,2,4,4-tetrahydrodibenzofuran (3, n = 1) was applied to the synthesis of 2,3-dihydro-1H-8-oxa-cyclopenta[a]indene (3, n = 0).

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The synthesis of compounds of Formula I where Z is CO, X is O, S(O)_p, CH₂, CO, NR⁶, R⁵ is OH, SH, and R¹, R², R³, and R⁴ and n are as defined above, can be made by the route shown in Scheme 2. The heterocycle (4) is acylated using Friedel-Crafts conditions with a compound of formula (6), prepared according to known methods such as, for example, as reported by Beckett et al., *Synlett.*, 1993:137, or the corresponding anhydride of formula (5) in the presence of a Lewis acid such as, for example, FeCl₃, AlCl₃, ZnCl₂, SnCl₄, and the like either neat or in an inert solvent such as dichloromethane, 1,2-dichloroethane, nitrobenzene, and the like at about -40°C to about 120°C to give a compound of formulas (7 and 8). A compound of formula (7) can be deprotected using standard methodology known to one skilled in the art to give the corresponding carboxylic acid (8), which can then be condensed with R⁷NH₂ to give a compound of formula (9). Alternatively, the carboxylic acid can be coupled with hydrogen sulfide after pretreatment with a suitable coupling agent such as, for example, 1,1'-carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC), and the like, and then condensed with R⁷NH₂ to give a compound of formula (12). Compound (9) can be treated with a protected hydroxylamine derivative such as O-benzylhydroxylamine to give the protected hydroxamic acid derivative (10). This can be deprotected by hydrogenolysis using a catalyst, such as palladium/BaSO₄ and hydrogen gas to give the hydroxamic acid (11).

The synthesis of compounds of Formula I where R² and R⁴ are hydrogen, Z is CO, X is O, S(O)_p, CH₂, CO, NR⁶, R⁵ is OH, SH, and R¹ and R³ and n are as defined above, can be made by the route shown in Scheme 3.

In Scheme 3, (R)- or (S)-4-benzyl-2-oxazolidinone can be reacted with an acid chloride (13), prepared using standard methodology known to one skilled in the art, in the presence of a non-nucleophilic base such as, for example, sodium hydride and the like in an inert solvent such as, for example, tetrahydrofuran and the like at temperatures between about -40°C and about reflux to give the N-acyl-oxazolidinone (14). The N-acyl-oxazolidinone (14) can be reacted with a suitable base such as, for example, potassium hexamethyldisilazide (KHDMS), lithium

diisopropylamide (LDA), and the like followed by a bromoester (15), prepared in racemic form by bromination of the corresponding ester (16) with a suitable brominating reagent such as, for example, N-bromosuccinimide (NBS) and the like in a suitable solvent such as, for example, carbon tetrachloride and the like in the presence of ultraviolet light and a peroxide such as, for example, benzoyl peroxide and the like or in chiral form by reaction of an amino acid (17) with sodium nitrite and potassium bromide in aqueous hydrobromic acid followed by reacting the resulting bromoacid with a suitable coupling agent such as, for example, CDI, DCC, $i\text{-C}_4\text{H}_9\text{OCOCl}$, and the like and reacting the activated acid with a suitable alcohol such as, for example, methanol, ethanol, benzyl alcohol, and the like to give a compound of formula (18). A compound of formula (18), which may exist as a mixture of diastereoisomers, can be purified by a suitable technique such as, for example, chromatography on silica gel, and the like to give pure stereoisomers ($\text{PG} = t\text{-Bu}$ or CH_2Ph), which can be reacted with lithium hydroxide in THF-water followed by reaction of the resulting carboxylic acid with oxalyl chloride to give the corresponding acid chloride (19).


The acid chloride (19) is then reacted with a heterocycle of formula (4) using Friedel-Crafts conditions (as previously described) to give compound (20), which can be deprotected using methods known in the art to give compounds of formula (21).

The synthesis of compounds of Formula I where R^1 , R^2 , R^3 (or R^4) are hydrogen, Z is CO, X is O, $\text{S}(\text{O})_p$, CH_2 , CO, NR^6 , R^5 is OH, and R^4 (or R^3) and n are as defined above, can be made by the route shown in Scheme 4. Friedel-Crafts acylation, in the presence of a Lewis acid such as, for example, FeCl_3 , AlCl_3 , ZnCl_2 , SnCl_4 , and the like either neat or in an inert solvent such as dichloromethane, 1,2-dichloroethane, nitrobenzene, and the like at about -40°C to about 120°C , of the heterocycle (4) with bromoacetyl bromide gives compound (22). This is then condensed with the enolate of diethyl malonate (generated by treating diethyl malonate with a metal hydride, such as sodium hydride, in a solvent such as THF or diethyl ether at temperatures ranging from

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-10°C to about 40°C) to yield compound (23). This can be alkylated by deprotonation with a metal hydride, such as sodium hydride, in a solvent such as DMF at temperatures ranging from -10°C to about 40°C followed by treatment with an alkylating agent ($R^3(4)X$) to yield compound (24). Hydrolysis of the ester groups can be achieved by treatment with lithium hydroxide in a solvent such as dioxane at temperatures ranging from -10°C to about 40°C to give the corresponding diacid (25). Decarboxylation occurs by heating compound (25) in a solvent such as toluene with a base such as triethylamine, to give compound (26) which can then be condensed with R^7NH_2 to give a compound of formula (27).

Alternatively, as shown in Scheme 5, esters (28) can be alkylated by treatment with a base, such as lithium diisopropylamide in a solvent such as THF or diethyl ether at temperatures ranging from -80°C to about 10°C, and tert-butyl bromoacetate (29) to give the diester (30). This could be selectively deprotected using trifluoroacetic acid in the presence of a suitable carbonium ion scavenger such as, for example, anisole, thioanisole, triethylsilane, and the like in a solvent such as dichloromethane, chloroform, and the like, to give the ester acid (31). This can then be converted to the corresponding acid chloride (32) by treatment with a chlorinating agent such as oxalyl chloride or thionyl chloride in a solvent such as dichloromethane. Friedel-Crafts acylation, in the presence of a Lewis acid such as, for example, $FeCl_3$, $AlCl_3$, $ZnCl_2$, $SnCl_4$, and the like either neat or in an inert solvent such as dichloromethane, 1,2-dichloroethane, nitrobenzene, and the like at about -40°C to about 120°C, of the heterocycle (4) with (32) gives compound (33). The ethyl ester is hydrolyzed by treatment with lithium hydroxide in a solvent such as dioxane at temperatures ranging from -10°C to about 40°C to give the corresponding acid (34) which can then be condensed with R^7NH_2 to give a compound of formula (35).

Alternatively, compounds of Formula I wherein Z is , R^5 is OH or

SH, and R^1 , R^2 , R^3 , R^4 , X, and n are as defined in Formula I, can be synthesized according to the sequence outlined in Scheme 6.

In Scheme 6 the heterocycle (4), prepared according to the procedure outlined in Scheme 1, is allowed to react with a suitable acylating agent such as, for example, the acid chloride of formula (13) and the like in the presence of a Lewis acid such as, for example, FeCl_3 , AlCl_3 , ZnCl_2 , and the like either neat or
5 in an inert solvent such as, for example, dichloromethane, nitrobenzene, and the like at about -40°C to about 120°C to give a compound of formula (36). A compound of formula (36) is allowed to react with a suitable strong base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran,
10 diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (37), or N-fluorodibenzenesulfonamide (NFSI) for R^2 equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of formula (38). A compound of formula (38) is allowed to react with a suitable strong base such as, for example, n-butyl lithium, lithium diisopropylamide,
15 potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (39) to give a compound of formula (40). A compound of formula (40) is deprotected using appropriate conditions such as, for example, trifluoroacetic acid or anhydrous hydrogen
20 chloride in a suitable solvent such as, for example, dichloromethane or chloroform, with or without a carbonium ion scavenger such as, for example, triethylsilane, and the resulting carboxylic acid is resolved using methods known to one skilled in the art to give a compound of formula (41). A compound of formula (41) is condensed with R^7NH_2 to give a compound of formula (42).
25 Alternatively, a compound of formula (41) is allowed to react with hydrogen sulfide after pretreatment with a suitable coupling agent such as, for example, 1,1'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide, isobutryl chloride, and the like, and then condensed with R^7NH_2 to give a compound of formula (43).

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Alternatively, a compound of formula (40) is allowed to react with a suitable base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C

5 followed by a suitable alkylating agent of formula (44) or NFSI for R³ equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of formula (45). A compound of formula (45) is deprotected using appropriate conditions such as, for example, trifluoroacetic acid or anhydrous hydrogen chloride in a suitable solvent such as, for example, dichloromethane or

10 chloroform, with or without a carbonium ion scavenger such as, for example, triethylsilane, and the resulting carboxylic acid is resolved using methods known to one skilled in the art to give a compound of formula (46). A compound of formula (46) is converted to compounds of formulas (47) and (48) according to the procedure described for the conversion of a compound of formula (41) to

15 compounds of formulas (42) and (43), respectively. Alternatively, a compound of formula (45) is allowed to react with a suitable base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (49)

20 or NFSI for R⁴ equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of formula (50). A compound of formula (50) is deprotected using appropriate conditions such as, for example, trifluoroacetic acid or anhydrous hydrogen chloride in a suitable solvent such as, for example, dichloromethane or chloroform, with or without a carbonium ion scavenger such

25 as, for example, triethylsilane, and the resulting carboxylic acid is resolved using methods known to one skilled in the art to give a compound of formula (51). A compound of formula (51) is converted to compounds of formulas (52) and (53) according to the procedure described for the conversion of a compound of formula (41) to compounds of formulas (42) and (43), respectively.

Alternatively, compounds of Formula I wherein Z is $\text{C}=\text{O}$, R^5 is OH or

SH, and, R^1 , R^2 , R^3 , R^4 , X, and n are as defined in Formula I are synthesized according to the sequence outlined in Scheme 7.

In Scheme 7, a compound of formula (54) is allowed to react with a
5 suitable base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (44) or NFSI for R^3 equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of
10 formula (55). A compound of formula (55) is allowed to react with a suitable base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (56), prepared by allowing a compound
15 of formula (4) to react with a suitable acylating agent such as BrCH_2COCl in the presence of a suitable Lewis acid such as, for example, FeCl_3 , AlCl_3 , ZnCl_2 , and the like either neat or in an inert solvent such as, for example, dichloromethane, nitrobenzene, and the like at about -40°C to about 120°C , to give a compound of formula (57). A compound of formula (57) is deprotected using appropriate
20 conditions such as, for example, trifluoroacetic acid or anhydrous hydrogen chloride in a suitable solvent such as, for example, dichloromethane or chloroform, with or without a carbonium ion scavenger such as, for example, triethylsilane, and the resulting carboxylic acid can be resolved using methods known to one skilled in the art to give a compound of formula (58). A compound
25 of formula (58) is converted to compounds of formulas (59) and (60) according to the procedure described in Scheme 6 for the conversion of a compound of formula (41) to compounds of formulas (42) and (43), respectively. Alternatively, a compound of formula (57) is allowed to react with a suitable base such as, for example, n-butyl lithium, lithium diisopropylamide, potassium

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hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (61), or NFSI for R² equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of formula (62). A
5 compound of formula (62) is deprotected using appropriate conditions such as, for example, trifluoroacetic acid or anhydrous hydrogen chloride in a suitable solvent such as, for example, dichloromethane or chloroform, with or without a carbonium ion scavenger such as, for example, triethylsilane, and the resulting carboxylic acid can be resolved using methods known to one skilled in the art to give a
10 compound of formula (63). A compound of formula (63) is converted to compounds of formulas (64) and (65) according to the procedure described in Scheme 6 for the conversion of a compound of formula (41) to compounds of formulas (42) and (43), respectively. Alternatively, a compound of formula (62) is allowed to react with a suitable base such as, for example, n-butyl lithium, lithium
15 diisopropylamide, potassium hexamethyldisilazide, and the like in an inert solvent such as, for example, tetrahydrofuran, diethyl ether, and the like at about -78°C to about 25°C followed by a suitable alkylating agent of formula (66), or NFSI for R¹ equals fluorine, at temperatures at about -78°C to about 50°C to give a compound of formula (50). A compound of formula (50) is converted via a
20 compound of formula (51) to compounds of formulas (52) and (53) according to the procedure described in Scheme 6.

Compounds of Formula I wherein Z is CH(OH), C=S, CF₂, or CHF, and R⁵ is OH or SH, and R¹, R², R³, R⁴, X, and n are as defined in Formula I are synthesized according to the sequence outlined in Scheme 8.

25 In Scheme 8, keto-esters of formulas (7), (40), (45), (50), (57), or (62) can be hydrolyzed to the corresponding keto-acids, such as by stirring in aqueous hydrochloric acid at a concentration between about 2 M and about 6 M and at temperatures between about 25°C and reflux or by stirring in the presence of a suitable alkali metal hydroxide such as, for example, lithium, sodium, potassium
30 hydroxide and the like in a suitable solvent such as, for example, methanol,

ethanol, aqueous THF and the like at temperatures between about 0°C and reflux followed by acidification, and the keto-acids can be reduced using an appropriate hydride donating reagent such as sodium borohydride in ethanol, L- or S-selectride and the like in a suitable solvent such as, for example, toluene, tetrahydrofuran and the like to give the alcohol-acid (67). The alcohol-acid (67) can be silylated such as, for example, by allowing it to react with chlorotrimethylsilane (TMS-Cl) in the presence of a catalyst such as, for example, imidazole and the like in a suitable solvent such as, for example, anhydrous dimethylformamide (DMF) and the like to give the corresponding O-silyl alcohol-silyl ester, which can be fluorinated by allowing it to react with a suitable reagent such as, for example, diethylaminosulfur trifluoride (DAST) and the like in a suitable solvent such as, for example, dichloromethane, chloroform and the like at temperatures between about -20°C and about reflux to give the corresponding fluoro-silyl ester, which can be hydrolyzed by stirring in aqueous hydrochloric acid at a concentration between about 2 M and about 6 M and at temperatures between about 25°C and reflux or by stirring in the presence of a suitable alkali metal hydroxide such as, for example, lithium, sodium, potassium hydroxide and the like in a suitable solvent such as, for example, methanol, ethanol, aqueous THF and the like at temperatures between about 0°C and reflux followed by acidification or by stirring in the presence of a suitable fluoride reagent such as, for example, tetra-n-butylammonium fluoride, aqueous hydrogen fluoride and the like in a suitable solvent such as, for example, tetrahydrofuran, acetonitrile and the like to give the fluoro-acid (68). The fluoro-acid (68) can be reacted with a suitable coupling agent such as, for example, CDI, DCC, i-C₄H₉OCOCl, and the like followed by hydrogen sulfide to give the fluoro-thioacid (69).

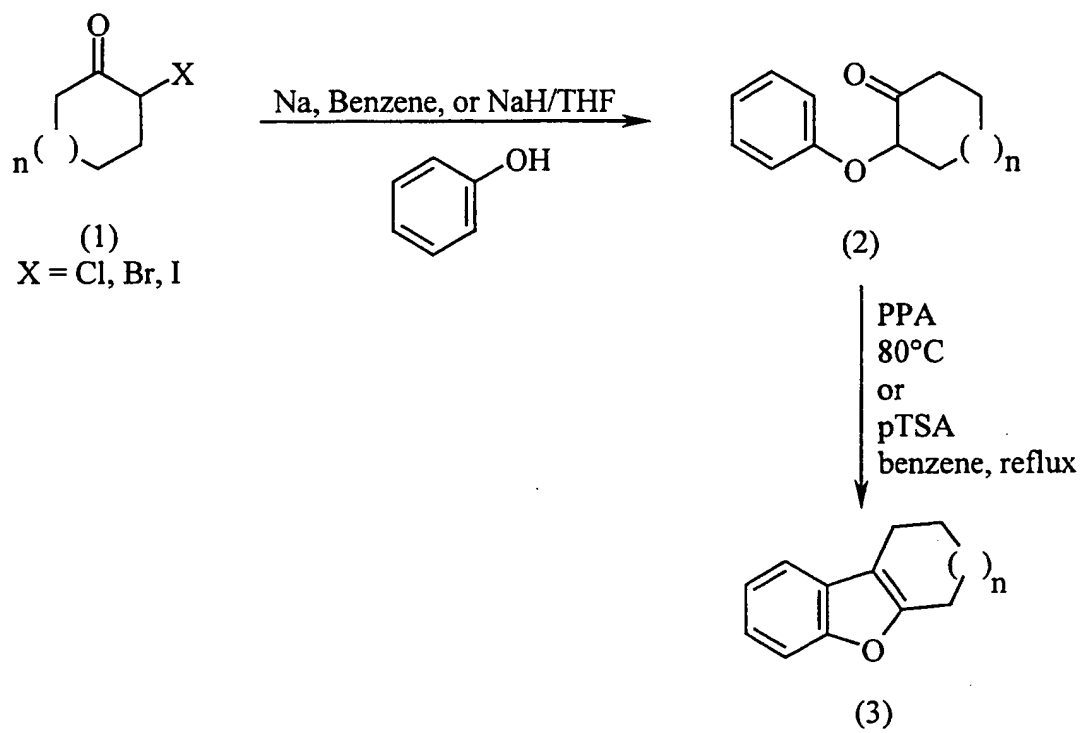
Alternatively, the keto-esters of formulas (7), (40), (45), (50), (57), or (62) can be allowed to react with a suitable fluorinating agent such as, for example, DAST and the like in a suitable solvent such as, for example, dichloromethane, chloroform and the like at temperatures between about -20°C and about reflux to give the corresponding fluoro-ester, which can be hydrolyzed such as by stirring in aqueous hydrochloric acid at a concentration between about 2 M and about 6 M

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and at temperatures between about 25°C and reflux or by stirring in the presence of a suitable alkali metal hydroxide such as, for example, lithium, sodium, potassium hydroxide and the like in a suitable solvent such as, for example, methanol, ethanol, aqueous THF and the like at temperatures between about 0°C and reflux followed by acidification to give the corresponding difluoro-acid (70). The difluoro-acid (70) can be allowed to react with a suitable coupling agent such as, for example, CDI, DCC, *i*-C₄H₉OCOCl, and the like followed by hydrogen sulfide to give the fluoro-thioacid (71).

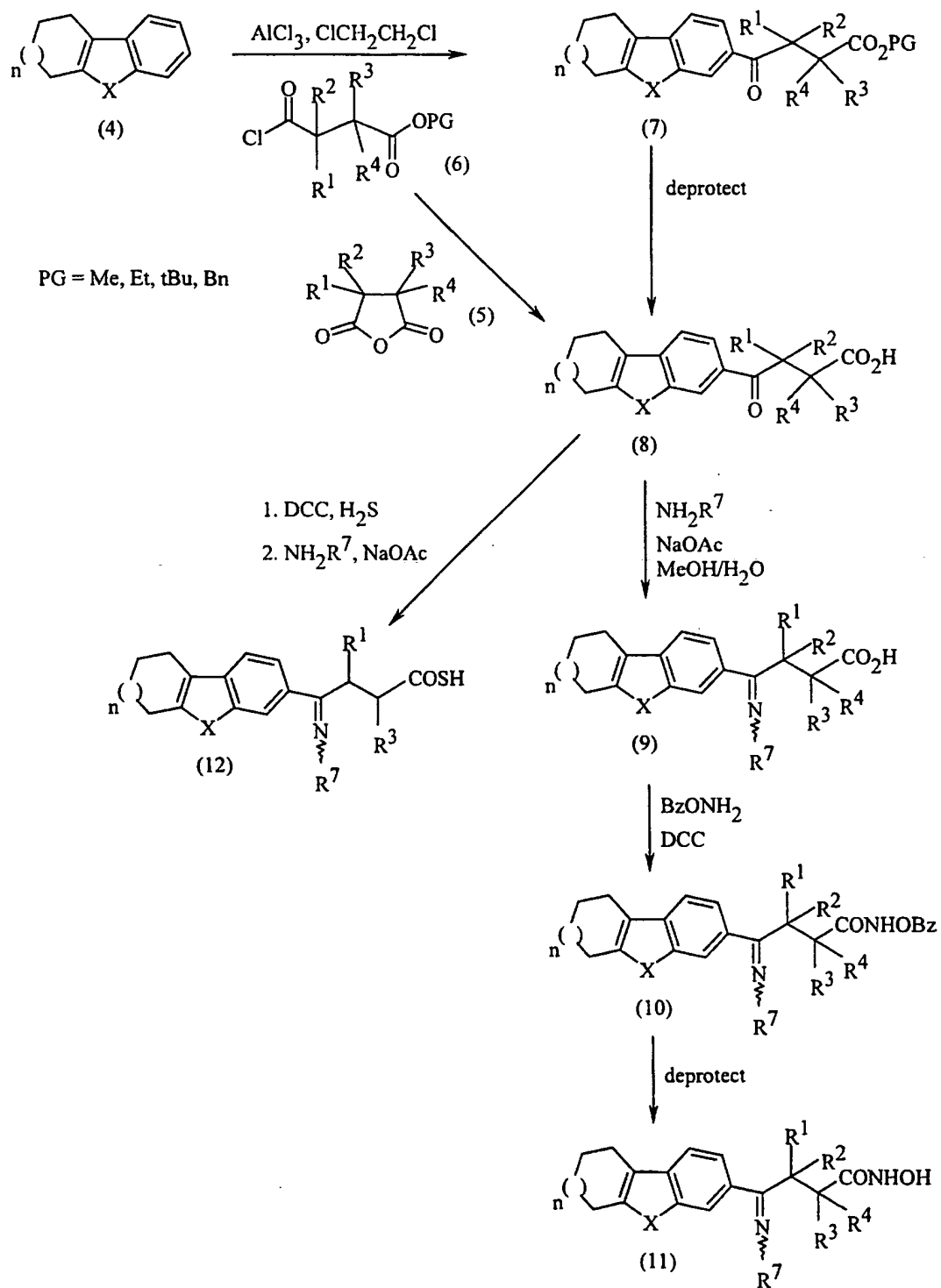
Alternatively, keto-esters of formulas (7), (40), (45), (50), (57), or (62) can be hydrolyzed to the corresponding keto-acids, such as by stirring in aqueous hydrochloric acid at a concentration between about 2 M and about 6 M and at temperatures between about 25°C and reflux or by stirring in the presence of a suitable alkali metal hydroxide such as, for example, lithium, sodium, or potassium hydroxide and the like in a suitable solvent such as, for example, methanol, ethanol, or aqueous THF and the like at temperatures between about 0°C and reflux followed by acidification, and the keto-acids allowed to react with a suitable sulfur reagent such as, for example, Lawesson's reagent and the like in a suitable solvent such as, for example, tetrahydrofuran and the like at temperatures between about 0°C and reflux to give the thioketo-acid (72). The thioketo-acid (72) can be allowed to react with a suitable coupling agent such as, for example, CDI, DCC, *i*-C₄H₉OCOCl, and the like followed by hydrogen sulfide to give the thioketo-thioacid (73).

Scheme 1



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Scheme 2

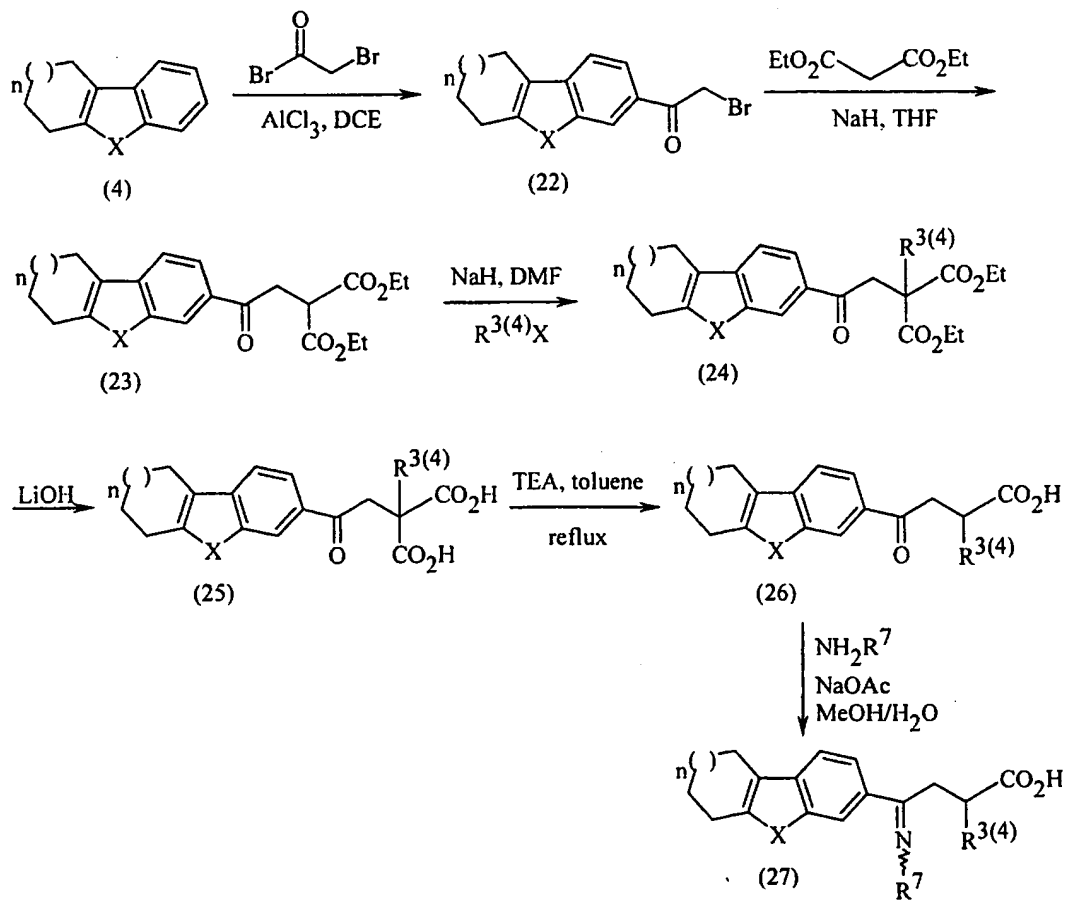


Scheme 3

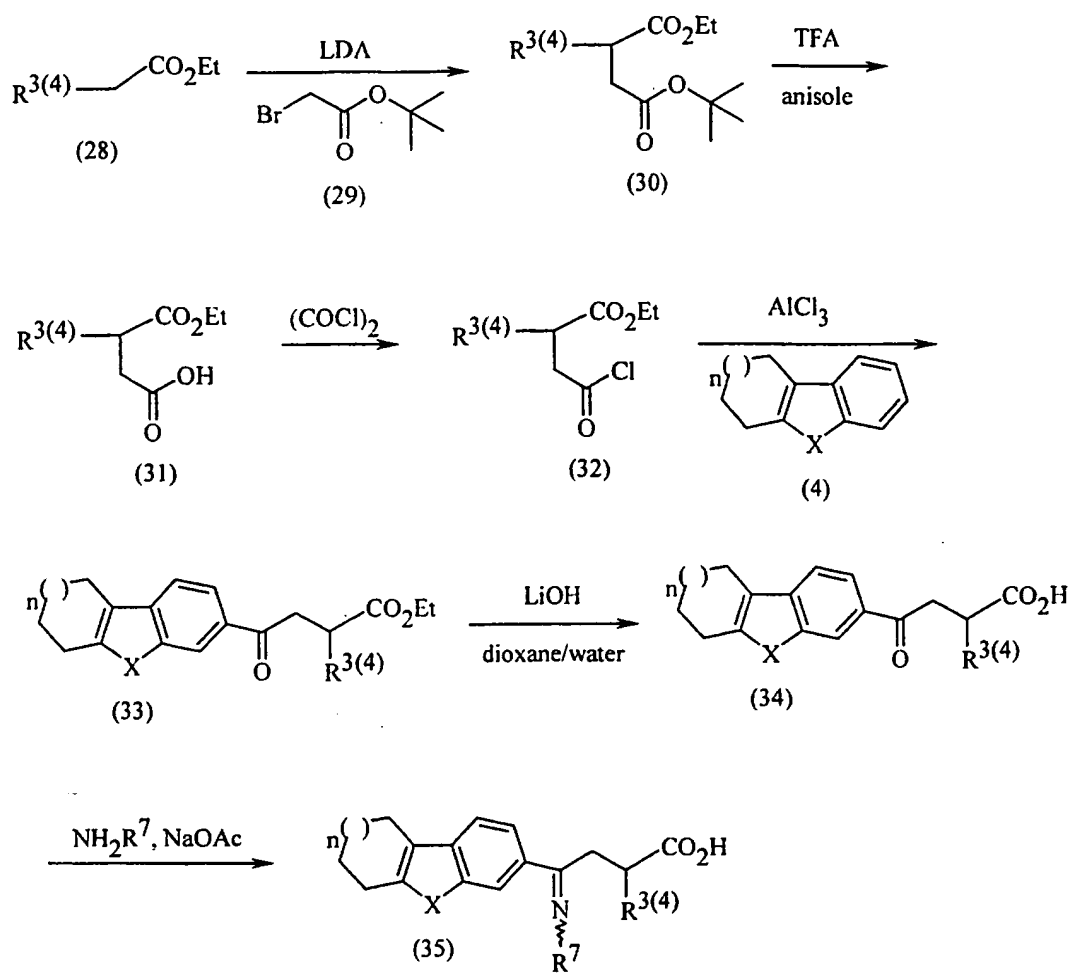


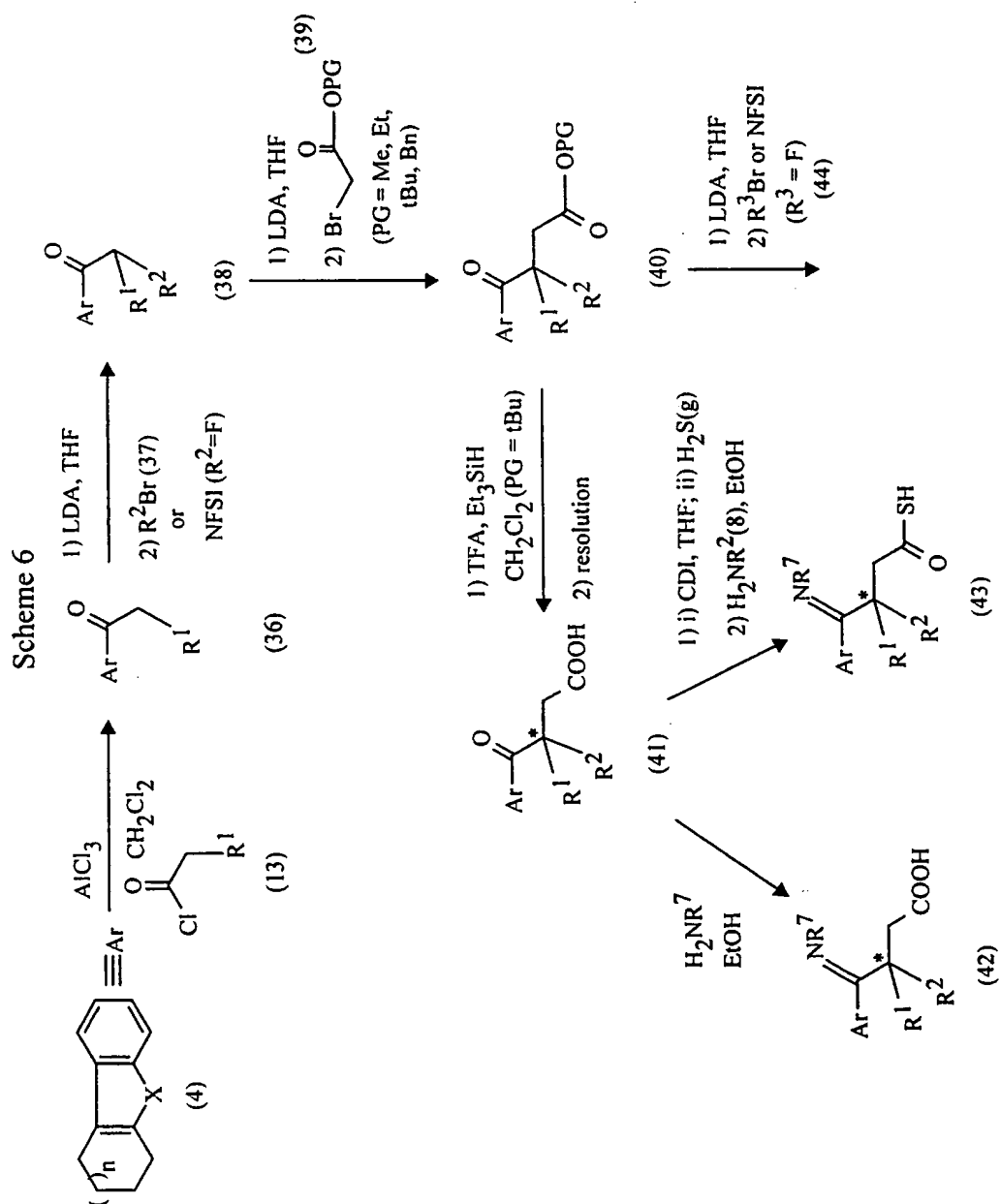
56

Scheme 4

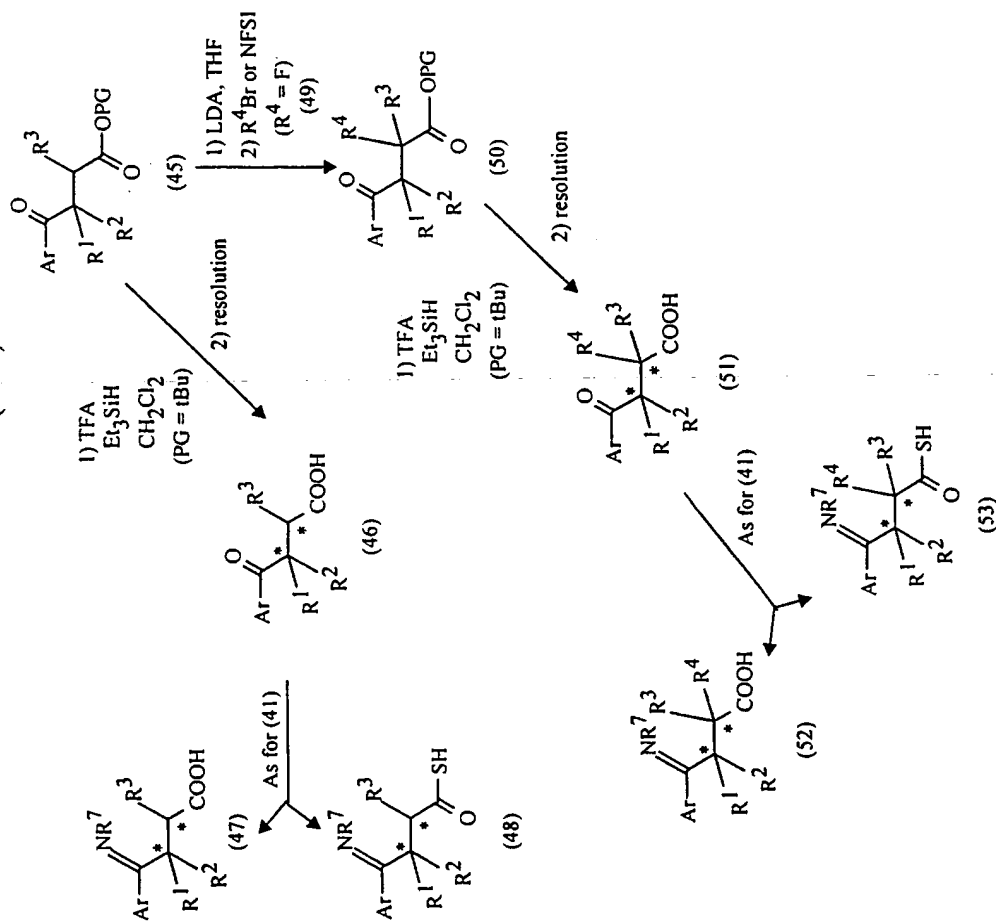


Scheme 5

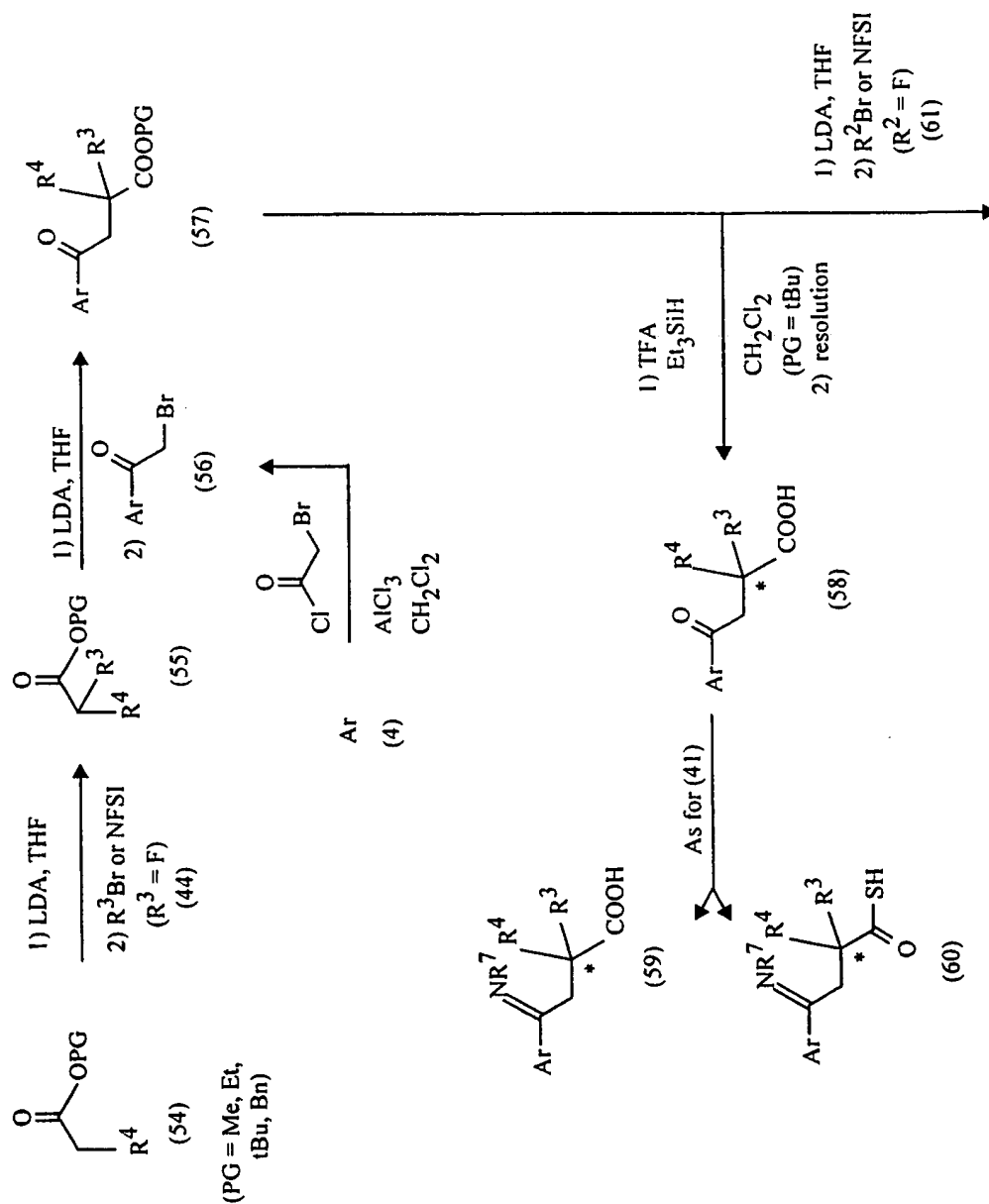




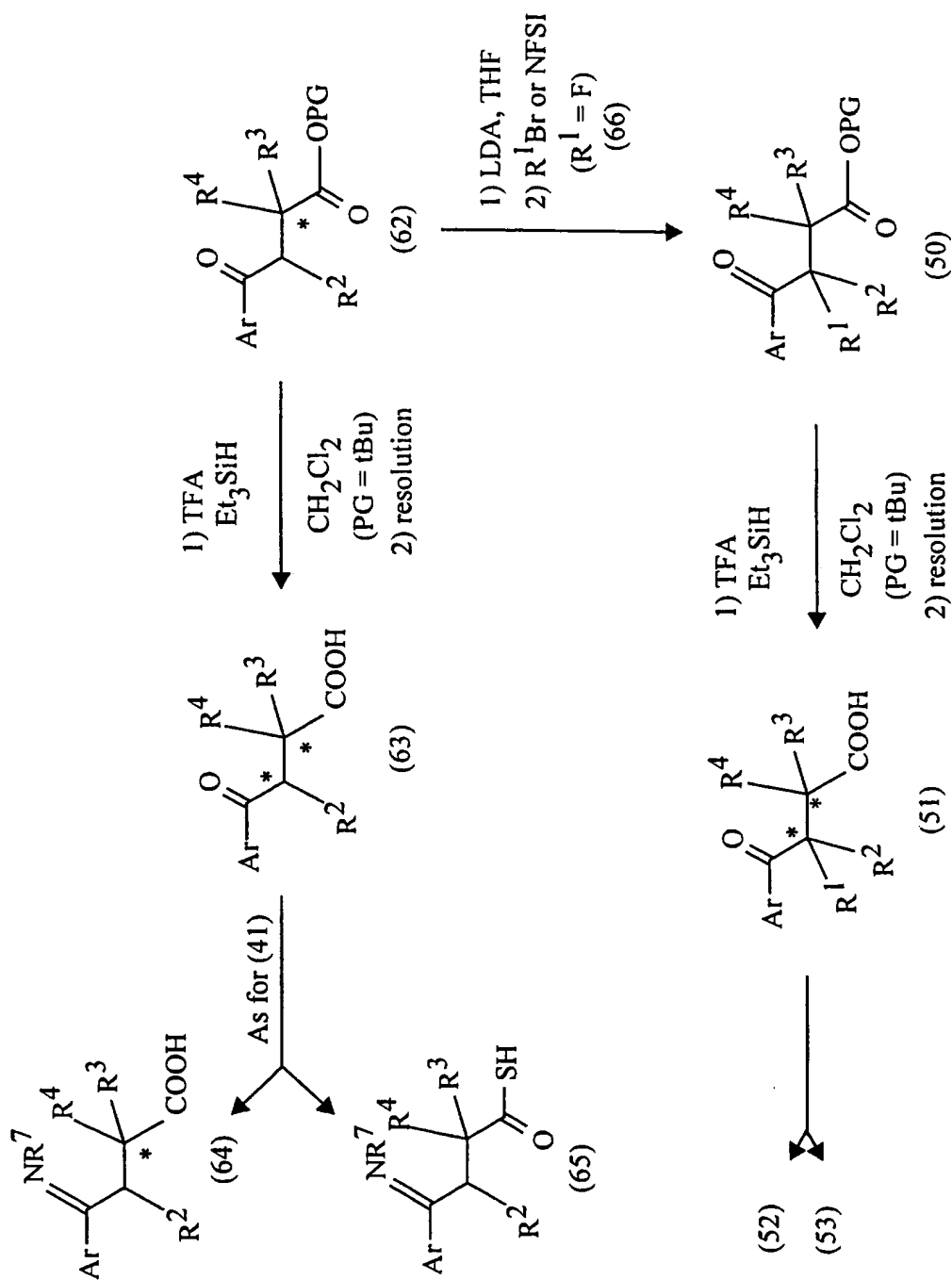
Scheme 6 (cont)



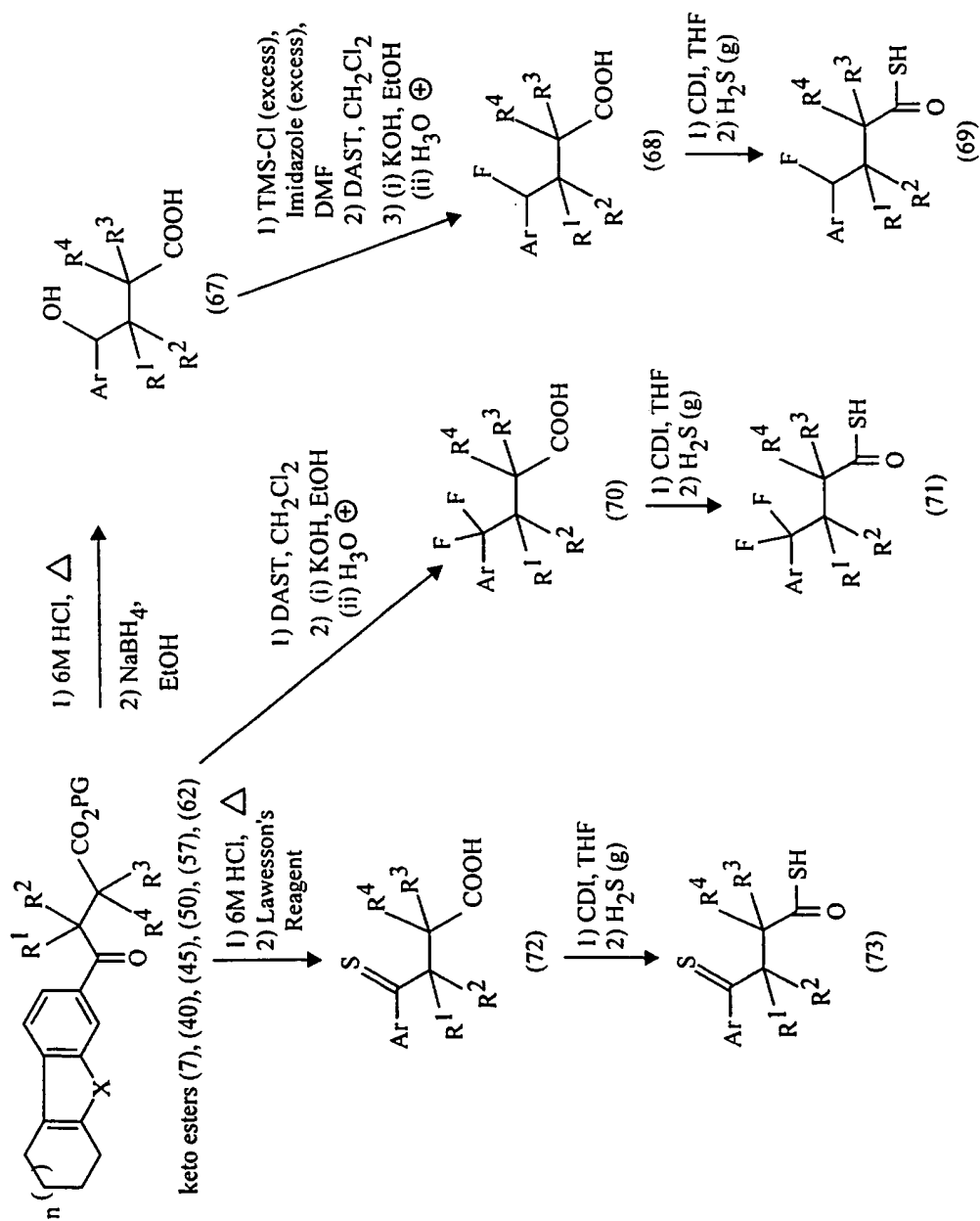
Scheme 7



Scheme 7 (cont)



Scheme 8



Compounds of formulas 5, 6, 8, 13, 15, 16, 17, 29, 37, 39, 44, or 49 are either commercially available or can be obtained by methods known in the art.

5 The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be
10 obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or
15 liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

20 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

25 The powders and tablets preferably contain from 5 or 10 to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the
30 active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are

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included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

5 In therapeutic use as agents for the treatment of multiple sclerosis, atherosclerotic plaque rupture, aortic aneurism, heart failure, left ventricular dilation, restenosis, periodontal disease, corneal ulceration, treatment of burns, decubital ulcers, wound healing, cancer, inflammation, pain, arthritis, osteoporosis, renal disease, or other autoimmune or inflammatory disorders
10 dependent upon tissue invasion by leukocytes, or other activated migrating cells, acute and chronic neurodegenerative disorders including stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's disease, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy, the compounds
15 utilized in the pharmaceutical methods of the invention are administered at the initial dosage of about 1 mg to about 100 mg per kilogram daily. A daily dose range of about 25 mg to about 75 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed.
20 Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions
25 during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid

30 To a methanolic solution (50 mL) of 4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid (Keumi T., Saga H., Shimakawa S., et al., *Fufui*

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Daigaku, Kogakubu Seni Kogyu Kenkyu Shisetsu Hokoku, 1976;14:71-7

(mp 143-146°C; mp 148.5-149.5°C (lit.)) (0.6 g, 0.0022 mol) and sodium acetate trihydrate (0.9 g, 0.0066 mol) at room temperature with stirring was added an aqueous solution (10 mL) of hydroxylamine hydrochloride (0.31 g, 0.0044 mol).

5 The resulting solution was heated to reflux for 4 hours. The solution was then cooled to room temperature and concentrated in vacuo. The residue was recrystallized from ethyl acetate/hexane (1:1) to yield the title compound (0.32 g, 51%) as a white solid; mp 164°C.

¹HNMR (DMSO-d₆) δ 7.8 (s, 1H), 7.5 (m, 1H), 7.43 (m, 1H), 2.95 (m, 2H), 2.71
10 (m, 2H), 2.56 (m, 2H), 1.85 (m, 2H), 1.76 (m, 2H) ppm.
MS (m+1) m/z 288.1.

EXAMPLE 2

2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid

15 Step (a) Preparation of: 2-(3-Phenyl-propyl)-succinic acid 4-tert-butyl ester 1-ethyl ester

To a solution of LDA (10.4 mL, 2 M in heptane/THF) in THF (20 mL), cooled to -70°C under N₂, was added dropwise ethyl 5-phenylvalerate (4 g, 19.4 mmol in 5 mL THF). The dark solution was stirred at -70°C for 30 minutes,
20 followed by the rapid addition of tert-butyl bromoacetate (4 g, 20.7 mmol in 5 mL THF). The reaction mixture was stirred at -70°C for 1 hour, then diluted with aqueous HCl (30 mL, 1 M) and ethyl acetate (30 mL). The organic phase was separated, washed with brine, dried (MgSO₄), and concentrated in vacuo. The resulting liquid was passed through a silica gel column (elution with hexane/ethyl
25 acetate (3:1)) to give the diester as a colorless liquid (2.4 g, 40%).

¹HNMR (CDCl₃) δ 7.3-7.1 (m, 5H), 4.2-3.8 (m, 3H), 2.6 (m, 2H), 1.6 (m, 4H), 1.4 (s, 9H), 1.2 (m, 5H) ppm.

Step (b) Preparation of: 2-(3-Phenyl-propyl)-succinic acid 1-ethyl ester

To a solution of anisole (0.9 g, 8.3 mmol) in trifluoroacetic acid (10 mL) was added dropwise the diester (2.4 g, 7.8 mmol) prepared in step (a). Hydrolysis of the tert-butyl ester was completed in 4 hours, at which time the solution was poured over ice, and the product was partitioned between diethyl ether and the aqueous acid. The organic phase was separated, dried (MgSO₄), and concentrated in vacuo leaving a viscous liquid. The product was purified using silica gel chromatography (elution with hexane/ethyl acetate (3:1)) to give the half-acid ester as a pale orange liquid (0.75 g, 38%).

¹HNMR (CDCl₃) δ 7.3-7.1 (m, 5H), 4.2 (m, 2H), 2.9-2.4 (m, 5H), 1.6 (m, 4H), 1.3 (m, 3H) ppm.

Step (c) Preparation of: 2-Chlorocarbonylmethyl-5-phenyl-pentanoic acid ethyl ester

The acid prepared in step (b) (0.73 g, 2.8 mmol) was diluted with dichloromethane (5 mL) and treated with oxalyl chloride (1.05 g, 8.3 mmol) in one portion. A catalytic amount of DMF was added, and the reaction mixture was stirred at room temperature for 16 hours. The solution was concentrated to dryness leaving an orange liquid (0.7 g, 78%).

¹HNMR (CDCl₃) δ 7.3-7.1 (m, 5H), 4.2 (m, 2H), 3.3 (m, 1H), 2.9 (m, 2H), 2.6 (t, 2H), 1.6 (m, 4H), 1.3 (t, 3H) ppm.

Step (d) Preparation of: 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid ethyl ester

To a suspension of AlCl₃ (0.28 g, 2.1 mmol) in dichloroethane (10 mL) cooled to 0°C was added dropwise tetrahydro-dibenzofuran (0.30 g, 1.7 mmol). The reaction mixture was stirred for 15 minutes, followed by the addition of the acid chloride (0.5 g, 1.7 mmol) prepared in step (c). After stirring at room temperature for 16 hours, the reaction mixture was poured over ice and diluted with ethyl acetate (50 mL). The organic phase was separated, washed with brine, dried (MgSO₄), and concentrated to dryness. The resulting viscous liquid was

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filtered through a pad of silica gel (elution with hexane/ethyl acetate (9:1)) to yield a yellowish green liquid (0.37 g, 51%).

¹HNMR (CDCl₃) δ 8.0 (d, 1H), 7.9 (m, 1H), 7.4 (m, 1H), 7.3-7.1 (m, 5H), 4.2 (q, 2H), 3.5 (m, 1H), 3.1-2.9 (m, 2H), 2.8-2.5 (m, 6H), 2.0-1.6 (m, 8H), 1.2 (t, 3H) ppm.

Step (e) Preparation of: 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-pentanoic acid

The ester prepared in step (d) (0.36 g, 0.87 mmol) was suspended in p-dioxane/water (5 mL, 1:1) and treated with LiOH (0.091 g) in one portion. The reaction mixture was stirred at room temperature for 16 hours, followed by dilution with aqueous HCl (1 M, pH = 1). The product was partitioned between ethyl acetate and the aqueous acid, the organic phase separated, washed with brine, dried (MgSO₄), and concentrated in vacuo. The crude product was purified using silica gel chromatography (elution with hexane/ethyl acetate (3:1)) to give the title compound as a white solid (0.075 g, 22%); mp 142-144°C.

¹HNMR (CDCl₃) δ 8.0 (s, 1H), 7.8 (d, 1H), 7.4 (d, 1H), 7.3 (m, 3H), 7.1 (m, 2H), 3.5 (m, 1H), 3.2 (m, 2H), 2.8-2.6 (m, 6H), 2.0-1.6 (m, 8H) ppm.

EXAMPLE 3

4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-ylmethyl)-butyric acid

Step (a) Preparation of: 2-Bromo-1-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethanone

A suspension of AlCl₃ (1.2 g, 9 mmol) in dichloroethane (30 mL) was treated with tetrahydro-dibenzofuran (1.2 g, 6.9 mmol) and bromoacetyl bromide (1.7 g, 8.4 mmol), respectively. The reaction mixture was refluxed for 1 hour, cooled to room temperature, and poured over ice. The aqueous suspension was diluted with chloroform, the layers separated, and the organic portion washed with brine, dried (MgSO₄), and concentrated to dryness leaving a viscous liquid. The

crude product was purified using silica gel chromatography (elution with toluene) to give a pale yellow solid (0.58 g, 29%).

^1H NMR (CDCl_3) δ 8.1 (d, 1H), 7.9 (m, 1H), 7.5 (m, 1H), 4.5 (d, 2H), 2.8-2.6 (m, 4H), 2.0-1.8 (m, 4H) ppm.

5 Step (b) Preparation of: 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-malonic acid diethyl ester

To a solution of diethylmalonate (0.28 g, 1.7 mmol) in DMF (10 mL) stirred under an atmosphere of N_2 was added NaH over a period of 10 minutes.

10 Dissolution occurred after 15 minutes, at which time the bromoacetyl tetrahydro-dibenzofuran (0.5 g, 1.7 mmol) was added in one portion. The yellow solution was stirred at room temperature for 2 hours, then poured into water (150 mL). The product extracted with 2 portions of diethyl ether, the extracts combined, washed with water, dried (MgSO_4), and concentrated in vacuo leaving a viscous liquid.

15 The product was purified using silica gel chromatography (elution with hexane/ethyl acetate (3:1)) to give the malonate derivative as a colorless liquid (0.24 g, 38%).

^1H NMR (CDCl_3) δ 8.1 (d, 1H), 7.9 (m, 1H), 7.5 (m, 1H), 4.2 (m, 4H), 4.1 (m, 1H), 3.7 (m, 2H), 2.8-2.6 (m, 4H), 2.0-1.8 (m, 4H), 1.3 (m, 6H) ppm.

20 Step (c) Preparation of: 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-malonic acid diethyl ester

The malonate derivative prepared in step (b) was diluted with DMF (3 mL) and treated with 3-bromomethyl-1,5,5-trimethylhydantoin (0.14 g, 0.59 mmol).

25 The solution was stirred at room temperature under N_2 , followed by the addition of NaH (0.030 g, 0.75 mmol). The solution was stirred for 16 hours, then diluted with water and ethyl acetate. The organic phase was separated and washed with water, dried (MgSO_4), and concentrated in vacuo. The liquid was isolated and passed through a silica gel column (elution with hexane/ethyl acetate (3:1)) to yield a white solid (0.050 g, 15%).

-70-

^1H NMR (CDCl_3) δ 8.1 (d, 1H), 7.9 (m, 1H), 7.5 (m, 1H), 4.4 (d, 2H), 4.2 (m, 4H), 3.7 (d, 2H), 2.8 (s, 3H), 2.75-2.6 (m, 4H), 2.0-1.8 (m, 4H), 1.3 (s, 6H), 1.28 (t, 6H) ppm.

Step (d) Preparation of: 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-malonic acid

The compound prepared in step (c) (0.050 g, 0.09 mmol) was diluted with p-dioxane/ H_2O (3 mL) followed by the addition of LiOH monohydrate (0.095 g) in one portion. The reaction mixture was stirred at room temperature for 16 hours, then acidified (pH=1) using aqueous HCl (1 M). Ethyl acetate was added, the layers separated, and the organic portion dried (MgSO_4) and concentrated leaving a white foam. Trituration with hexane/ethyl acetate yielded the bis acid as a white solid (0.040 g, 89%).

CI-MS ($\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_8$) $[\text{M}+\text{H}]^+$ 470.

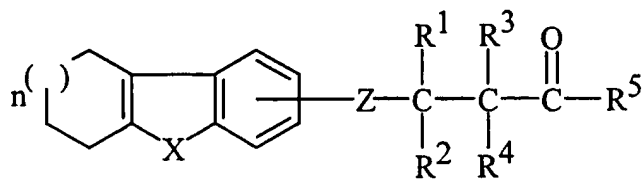
Step (e) Preparation of: 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolin-1-ylmethyl)-butyric acid

The bis acid prepared in step (d) (0.020 g, 0.042 mmol) was suspended in toluene (3 mL) and treated with one equivalent of triethylamine (4.3 mg, 0.042 mmol). The reaction mixture was refluxed for 2 hours, cooled, and concentrated in vacuo. The product was partitioned between ethyl acetate and aqueous HCl (1 M), the layers separated, and the organic portion dried (MgSO_4) and concentrated in vacuo. Trituration of the resulting foam with hexane/ethyl acetate (4:1) yielded the title compound (5 mg, 28%) as a cream colored solid.

^1H NMR (CDCl_3) δ 7.9 (d, 1H), 7.8 (m, 1H), 7.3 (m, 1H), 3.9-3.2 (m, 5H), 2.8 (s, 3H), 2.7-2.5 (m, 4H), 1.9-1.7 (m, 4H), 1.2 (s, 6H) ppm.

CLAIMS

1. A compound of Formula I



I

wherein n is zero or an integer of 1 or 2;

5

X is -O-,

-S(O)_p- wherein p is zero or an integer of 1 or 2,

-N- wherein R⁶ is hydrogen, alkyl, acyl, or benzyl,

|
R⁶

10

-CH₂-, or

-C-;

||
O

15

Z is -C-,
||
O

OH

|

-CH-,

20

S

||

-C-,

CF₂,

CHF,

25

-CH₂-,

N-R⁷

||

-C- wherein R⁷ is OR⁸ wherein R⁸ is hydrogen,

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alkyl,

-(CH₂)_m-aryl wherein m is zero or an integer of 1 to 6,

-(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above or

5 N-R⁹ wherein R⁹ and R^{9a} are either the same or

$$\begin{array}{c} | \\ \text{R}^{\text{9a}} \end{array}$$

different and are hydrogen,

alkyl,

10

aryl,

arylalkyl,

heteroaryl, or

cycloalkyl;

R^1, R^2, R^3 , and R^4 are either the same or different and are

15

hydrogen,

fluorine,

alkyl,

alkenyl,

alkynyl,

20

arylalkenyl,

heteroarylalkenyl,

arylalkynyl,

heteroarylalkynyl,

-(CH₂)_m-aryl wherein m is as defined above,

25

-(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above,

-(CH₂)_q-X^a-(CH₂)_q 1-alkyl wherein X^a is O, S, SO, SO₂, or NH,

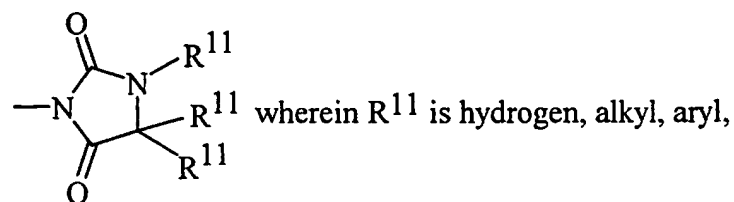
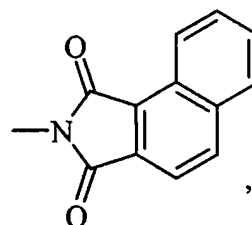
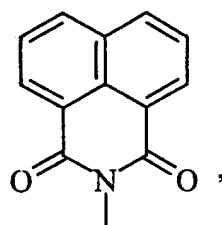
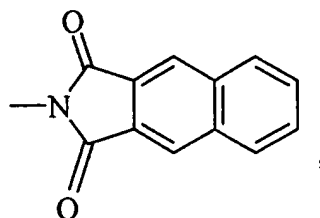
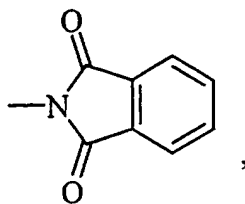
and q and q^1 are each zero or an integer of 1 to 6, and the

sum of $q + q^1$ is not greater than six,

$-(CH_2)_q-X^a-(CH_2)_{q^1}$ -aryl wherein X^a , q , and q^1 are as defined above,

$-(CH_2)_q-X^a-(CH_2)_{q^1}$ -heteroaryl wherein X^a , q , and q^1 are as defined above, or

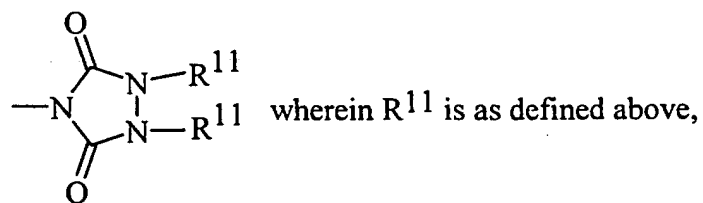
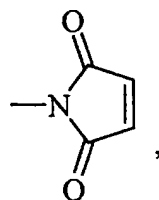
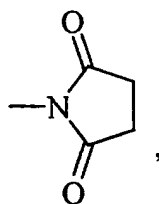
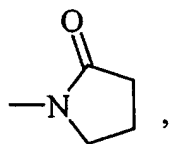
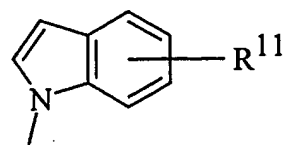
5 $-(CH_2)_m-R^{10}$ wherein R^{10} is



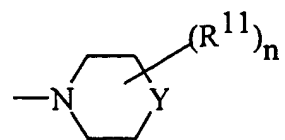
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arylalkyl, heteroaryl, or cycloalkyl,

-74-

wherein R¹¹ is as defined above,wherein R¹¹ is as defined above,

5



wherein Y is nitrogen, oxygen,

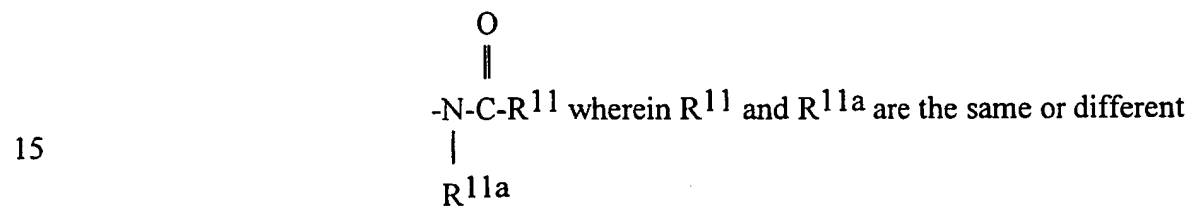
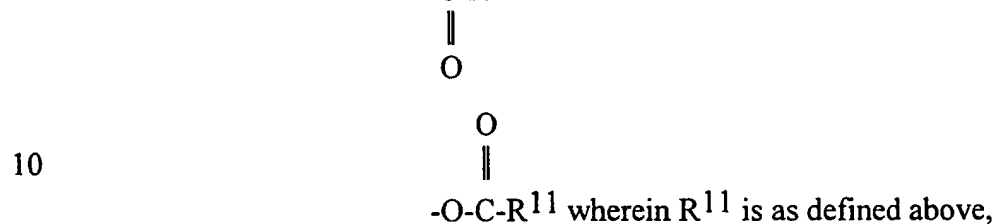
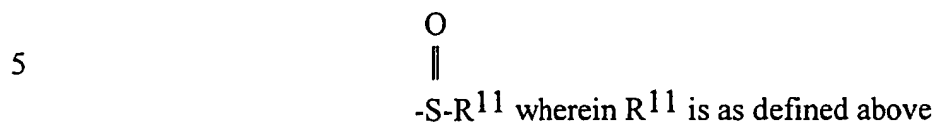
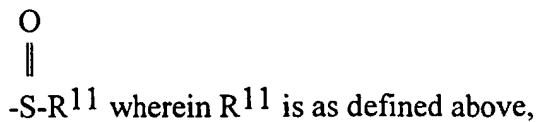
sulfur, or CH₂ and R¹¹ and n are as defined above

and m is as defined above,

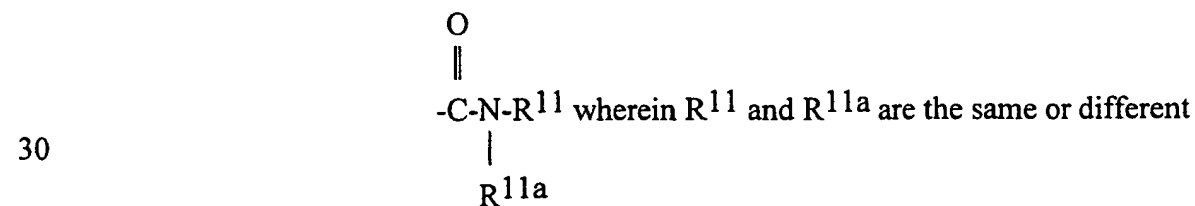
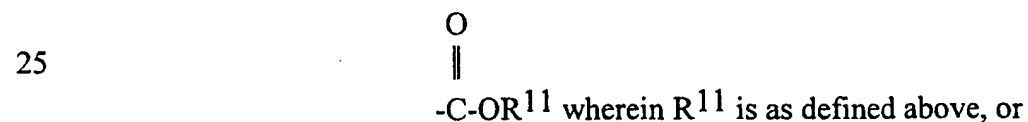
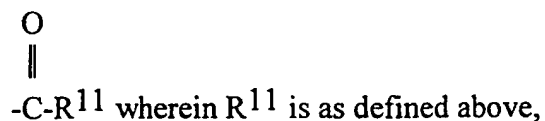
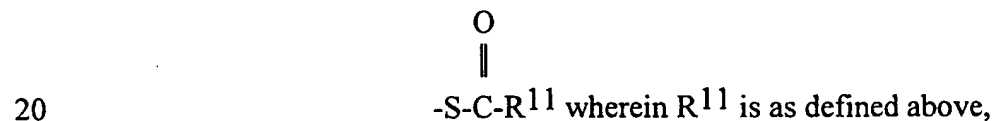
OR¹¹ wherein R¹¹ is as defined above,-N-R¹¹ wherein R¹¹ and R^{11a} are the same or different

10

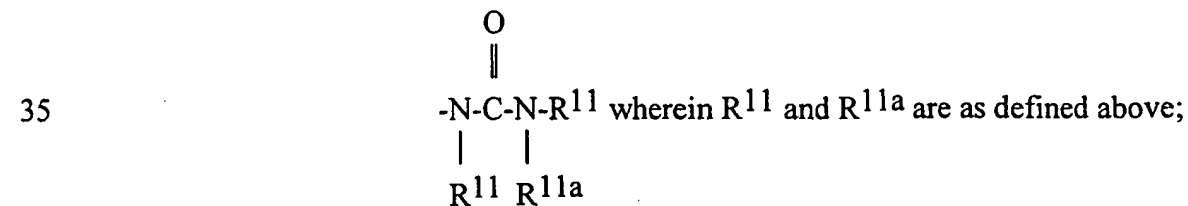
and are as defined above for R¹¹,-SR¹¹ wherein R¹¹ is as defined above,



and are as defined above for R^{11} ,



and are as defined above for R^6 , or



and

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R^5 is $-OR^{12}$ wherein R^{12} is hydrogen,

alkyl, or

benzyl,

$-NH-OR^{12}$ wherein R^{12} is as defined above, or

$-SH$;

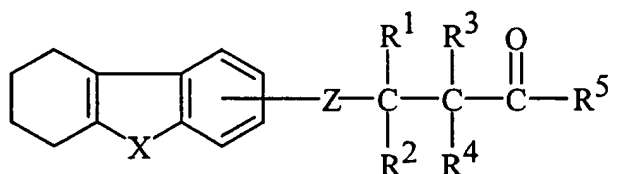
5

with the proviso that when n is 1, X is $-O-$, Z is $-C-$, and R^5 is OR^{12}

wherein R^{12} is as defined above, then at least one of R^1 , R^2 , R^3 , and R^4 is not hydrogen; and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.

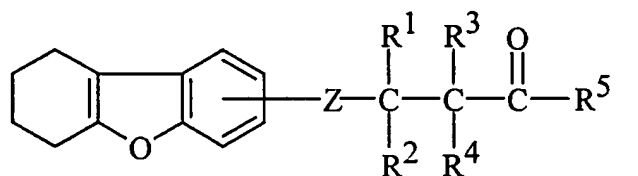
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2. The compound according to Claim 1 which is

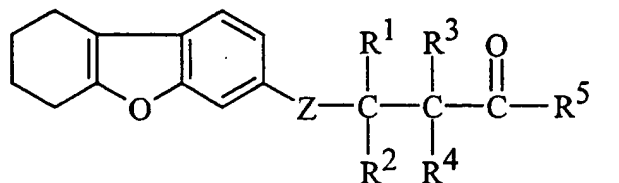


3. The compound according to Claim 1 which is

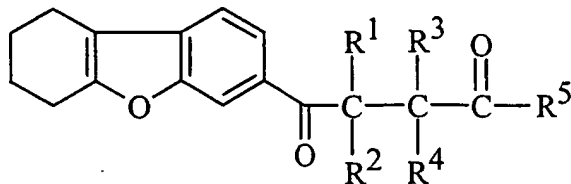
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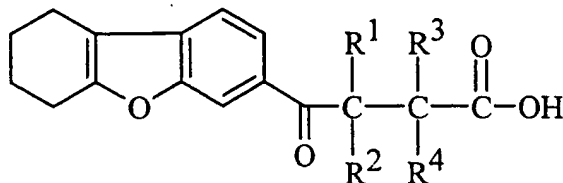
4. The compound according to Claim 1 which is



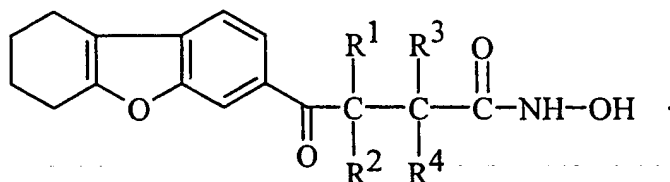
5. The compound according to Claim 1 which is



6. The compound according to Claim 1 which is



7. The compound according to Claim 1 which is



8. A compound selected from the group consisting of:

4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

N-Hydroxy-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyramide;

N-Hydroxy-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyramide;

4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-butyric acid;

4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-butyric acid;

4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;

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2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;

2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;

5 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;

(S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

10 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;

15 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;

(S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

20 (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

(S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

25 (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

30 (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 5 (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-2-phenethyl-butyric acid;
- 10 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid;
- 15 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-phenyl-octanoic acid;
- 20 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-phenyl-heptanoic acid;
- (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-phenyl-hexanoic acid;
- 25 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-phenyl-pentanoic acid;
- (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-phenethyl-butyric acid;
- (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyric acid;
- 30 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

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(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

5 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

10 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

15 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

20 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-oxo-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(1H-indol-3-ylmethyl)-4-oxo-butyric acid;

25 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-oxo-butyric acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

30 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-hydroxyimino-butyric acid;

5 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1H-indol-3-yl)-ethyl]-4-oxo-butyric acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

10 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

15 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

20 (S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-(1H-indol-3-ylmethyl)-butyric acid;

(S) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-[2-(1H-indol-3-yl)-ethyl]-butyric acid;

25 (S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

(S) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxy-butyric acid;

30 4-Hydroxy-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

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- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;
- 5 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;
- 4-Hydroxy-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 10 4-Hydroxy-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- 2-[2-Hydroxy-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 15 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxy-butyric acid;
- 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- 20 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- 25 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;
- 4-Hydroximino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 30

- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- 5 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;
- (S) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 10 (S) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 15 (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 20 (S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 25 (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;
- (S) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (S) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 30 (S) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;

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4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-butyric acid;

4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-butyric acid;

5 4-Oxo-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

10 (S) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

15 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

(S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

20 (S) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

25 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

(S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-butyric acid;

30 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-butyric acid;

- (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (S) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- 5 (S) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (S) 4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-phenethyl-butyrlic acid;
- (S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- 10 (S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- (S) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-8-phenyl-octanoic acid;
- 15 (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (S) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- 20 (S) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (S) 4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-2-phenethyl-butyrlic acid;
- (S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;
- 25 (S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;
- (S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid;
- 30 (S) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;

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(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-phenyl-pentanoic acid;

5 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-7-phenyl-heptanoic acid;

10 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

15 (R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

(R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

20 (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-butyric acid;

(R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-pentanoic acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

25 (R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

30 (R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

- (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzofuran-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-oxo-2-phenethyl-butyric acid;
- 5 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;
- 10 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-phenyl-octanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-phenyl-heptanoic acid;
- 15 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-phenyl-hexanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-phenyl-pentanoic acid;
- 20 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-phenethyl-butyric acid;
- (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-butyric acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;
- 25 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;
- (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;
- 30 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

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(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-butyric acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-hexanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-octanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-oxo-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(1H-indol-3-ylmethyl)-4-oxo-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-oxo-butyric acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-4-hydroxyimino-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-4-hydroxyimino-butyric acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-[2-(1H-indol-3-yl)-ethyl]-4-oxo-butyric acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

5 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-5-(1H-indol-3-yl)-pentanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-6-(1H-indol-3-yl)-hexanoic acid;

10 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-oxo-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

(R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-(1H-indol-3-ylmethyl)-butyric acid;

15 (R) 4-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-4-hydroxyimino-2-[2-(1H-indol-3-yl)-ethyl]-butyric acid;

(R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-8-(1H-indol-3-yl)-octanoic acid;

20 (R) 2-[2-(2,3-Dihydro-1H-8-oxa-cyclopenta[a]inden-6-yl)-2-hydroxyimino-ethyl]-7-(1H-indol-3-yl)-heptanoic acid;

(R) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;

25 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;

30 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;

- (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-phenyl-pentanoic acid;
- (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-6-phenyl-hexanoic acid;
- 5 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-8-phenyl-octanoic acid;
- (R) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- 10 (R) 4-Oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 15 (R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- 20 (R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-oxo-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 25 (R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-oxo-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;
- (R) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- (R) 2-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-4-hydroxyimino-4-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-butyric acid;
- 30 (R) 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-[2-hydroxyimino-2-(6,7,8,9-tetrahydro-5H-fluoren-2-yl)-ethyl]-pentanoic acid;

(R) 4-Oxo-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

5 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

10 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Hydroxyimino-2-phenethyl-4-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-butyric acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-5-phenyl-pentanoic acid;

15 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-6-phenyl-hexanoic acid;

(R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-7-phenyl-heptanoic acid;

20 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-5H-10-oxa-benzo[a]azulen-2-yl)-ethyl]-8-phenyl-octanoic acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;

(R) 4-Oxo-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;

25 (R) 2-[2-Oxo-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;

(R) 4-Hydroxyimino-4-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-phenethyl-butyric acid;

30 (R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-5-phenyl-pentanoic acid;

(R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-6-phenyl-hexanoic acid;

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- (R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-7-phenyl-heptanoic acid;
- (R) 2-[2-Hydroxyimino-2-(9-methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-ethyl]-8-phenyl-octanoic acid;
- 5 (R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-ylmethyl)-butyric acid;
- (R) 4-Hydroxyimino-4-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-2-[2-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-ethyl]-butyric acid;
- 10 (R) 2-[2-Hydroxyimino-2-(6,7,8,9-tetrahydro-dibenzothiophen-3-yl)-ethyl]-5-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)-pentanoic acid;
- (R) 4-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-4-oxo-2-phenethyl-butyric acid;
- (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-5-phenyl-pentanoic acid;
- 15 (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-6-phenyl-hexanoic acid;
- (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-7-phenyl-heptanoic acid; and
- (R) 2-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-carbazol-2-yl)-2-oxo-ethyl]-8-phenyl-octanoic acid;
- 20 and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof.
9. The method of inhibiting a matrix metalloproteinase comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 25 10. The method of inhibiting gelatinase A comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

11. The method of inhibiting stromelysin-1 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 5 12. The method of inhibiting collagenase-3 comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
13. The method of preventing atherosclerotic plaque rupture comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 10 14. The method of inhibiting aortic aneurysm comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 15 15. The method of inhibiting heart failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
16. The method of preventing restenosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 20 17. The method of controlling periodontal disease comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
18. The method of treating corneal ulceration comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

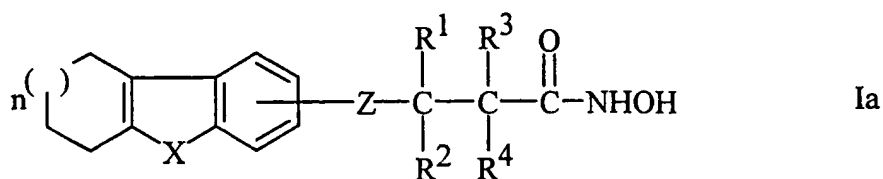
-94-

19. The method of treating burns comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 5 20. The method of treating decubital ulcers comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
21. The method of treatment for healing wounds comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 10 22. The method of treating cancer comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 15 23. The method of treating arthritis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
24. The method of treating osteoporosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 20 25. The method of treating autoimmune or inflammatory disorders dependent upon tissue invasion by leukocytes comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 25 26. The method of treating multiple sclerosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

27. The method of treating inflammation and pain comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 5 28. The method of treating acute and chronic neurodegenerative disorders selected from the group consisting of: stroke, head trauma, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, AIDS, Parkinson's disease, Huntington's diseases, prion diseases, myasthenia gravis, and Duchenne's muscular dystrophy comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 10 29. The method of treating renal disease comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 15 30. The method of treating left ventricular dilation comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
31. The pharmaceutical composition comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
- 20 32. The pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

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33. A method for preparing a compound of Formula Ia



wherein n is zero or an integer of 1 or 2;

X is -O-,

5 -S(O)_p- wherein p is zero or an integer of 1 or 2,-N- wherein R⁶ is hydrogen, alkyl, acyl, or benzyl,
$$\begin{array}{c} | \\ R^6 \end{array}$$
-CH₂-, or

10 -C-;

$$\begin{array}{c} || \\ O \end{array}$$

$$\begin{array}{c} O \\ || \end{array}$$

15 Z is -C-,

OH

|

-CH-,

S

||

20 -C-,

CF₂,

CHF,

-CH₂-,25 N-R⁷

||

-C- wherein R⁷ is OR⁸ wherein R⁸ is hydrogen,

alkyl,

-(CH₂)_m-aryl wherein m is zero or an integer of 1 to 6,30 -(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above or

N-R⁹ wherein R⁹ and R^{9a} are either the same or
|
R^{9a}

5

different and are hydrogen,

alkyl,

aryl,

arylalkyl,

heteroaryl, or

10

cycloalkyl;

R¹, R², R³, and R⁴ are either the same or different and are

hydrogen,

fluorine,

alkyl,

15

alkenyl,

alkynyl,

arylalkenyl,

heteroarylalkenyl,

arylalkynyl,

20

heteroarylalkynyl,

-(CH₂)_m-aryl wherein m is as defined above,

-(CH₂)_m-heteroaryl wherein m is as defined above,

-(CH₂)_m-cycloalkyl wherein m is as defined above,

-(CH₂)_q-X^a-(CH₂)_{q¹}-alkyl wherein X^a is O, S, SO, SO₂, or NH,

25

and q and q¹ are each zero or an integer of 1 to 6, and the

sum of q + q¹ is not greater than six,

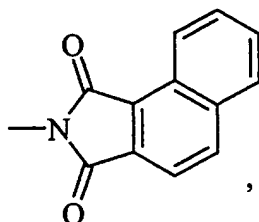
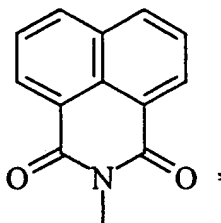
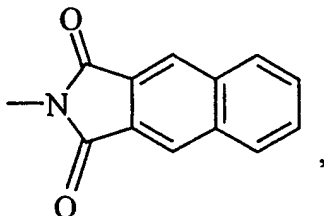
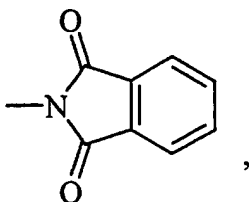
-(CH₂)_q-X^a-(CH₂)_{q¹}-aryl wherein X^a, q, and q¹ are as defined
above,

-(CH₂)_q-X^a-(CH₂)_{q¹}-heteroaryl wherein X^a, q, and q¹ are as

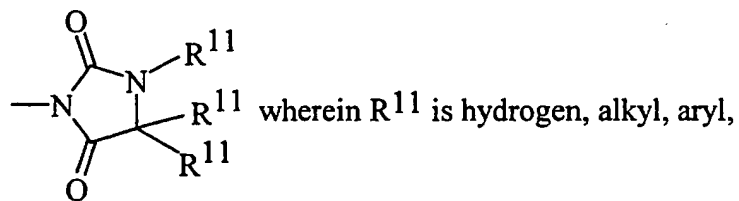
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defined above, or

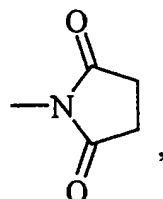
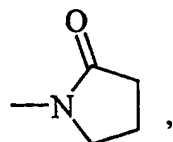
-98-

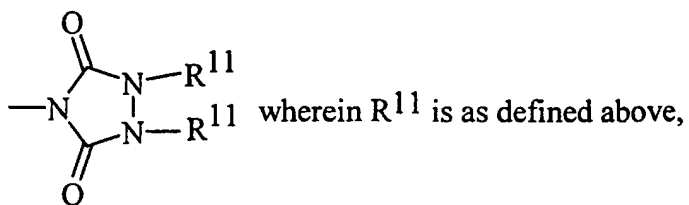
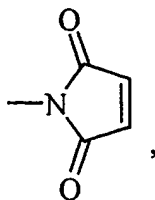
 $-(CH_2)_m-R^{10}$ wherein R^{10} is


5

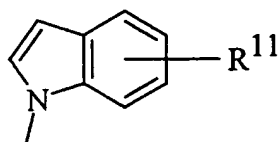


arylalkyl, heteroaryl, or cycloalkyl,

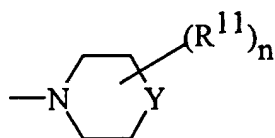




wherein R¹¹ is as defined above,



wherein R¹¹ is as defined above,



wherein Y is nitrogen, oxygen,

sulfur, or CH₂ and R¹¹ and n are as defined above

and m is as defined above,

OR¹¹ wherein R¹¹ is as defined above,

-N-R¹¹ wherein R¹¹ and R^{11a} are the same or different



and are as defined above for R¹¹,

-SR¹¹ wherein R¹¹ is as defined above,



-S-R¹¹ wherein R¹¹ is as defined above,

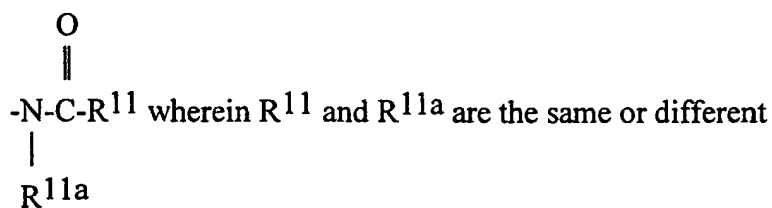
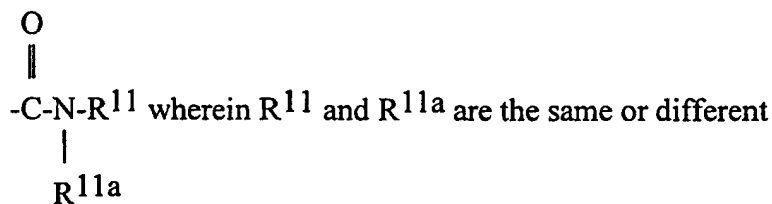
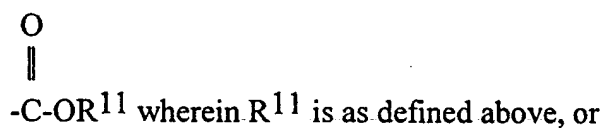
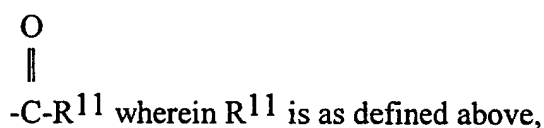
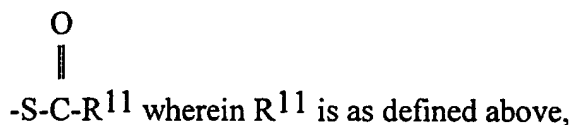
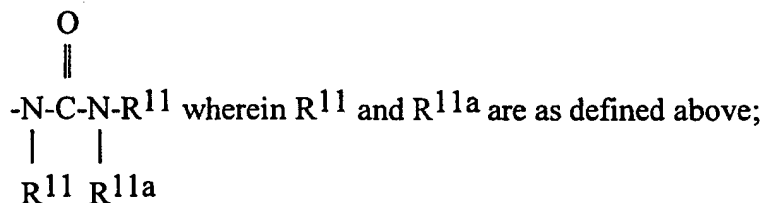


-S-R¹¹ wherein R¹¹ is as defined above

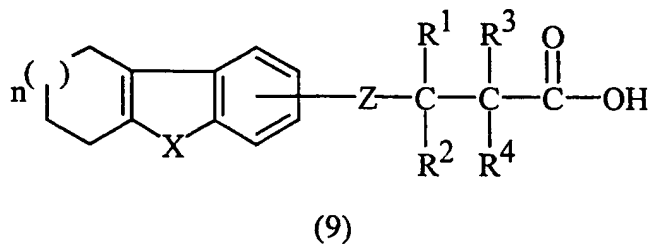


-O-C-R¹¹ wherein R¹¹ is as defined above,

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and are as defined above for R^{11} ,and are as defined above for R^6 , or

and corresponding isomers thereof; or a pharmaceutically acceptable salt thereof which comprises treating a compound of formula (9)



wherein n , X , Z , R^1 , R^2 , R^3 , and R^4 are as defined above with NH_2OBz in a solvent followed by deprotection to give a compound of Formula Ia

and if desired, converting a compound of compound of Formula Ia to a corresponding pharmaceutically acceptable salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable salt to a compound of Formula Ia by conventional means.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12272

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D307/91 C07D333/76 C07D209/86 C07D209/94 C07D209/80
 C07D233/78 C07C239/14 C07C59/205 C07C59/11 A61K31/34
 A61K31/38 A61K31/40 A61K31/13 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 38434 A (WARNER-LAMBERT CO.) 5 December 1996 (1996-12-05) claims 1-16, 32-34 ----	1-8, 31, 32
A	WO 98 06711 A (WARNER-LAMBERT CO.) 19 February 1998 (1998-02-19) claims 1-36 ----	1-8, 31, 32
A	WO 98 09957 A (WARNER-LAMBERT CO.) 12 March 1998 (1998-03-12) abstract; claims 1-12, 39 ----	1-8, 31, 32
A	WO 98 09934 A (WARNER-LAMBERT CO.) 12 March 1998 (1998-03-12) abstract; claims 34, 35 ----- -/--	1-8, 31, 32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 September 1999

Date of mailing of the international search report

15/10/1999

Name and mailing address of the ISA

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Authorized officer

Hass, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	P. CAGNIANT ET AL.: BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no. 12, 1971, pages 4435-42, XP002116957 page 4435, compound 2; page 4438, compounds 10 and 15 ---	1,2
A	CHEMICAL ABSTRACTS, vol. 88, no. 21, 22 May 1978 (1978-05-22) Columbus, Ohio, US; abstract no. 152329u, page 581; XP002116958 & T. KEUMI ET AL.: FUKUI DAIGAKU KOGAKUBU SENI KOGYO KENKYU SHISETSU HOKOKU, vol. 14, 1976, pages 71-7, -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/12272

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-30
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 9-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 9-30

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/12272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9638434 A	05-12-1996	US 5665764 A	09-09-1997
		US 5627206 A	06-05-1997
		AU 5577796 A	18-12-1996
		CA 2220040 A	05-12-1996
		EP 0828726 A	18-03-1998
		JP 11506097 T	02-06-1999
		ZA 9604508 A	09-12-1996
WO 9806711 A	19-02-1998	AU 3729397 A	06-03-1998
		EP 0923569 A	23-06-1999
		HR 970410 A	31-08-1998
WO 9809957 A	12-03-1998	AU 4177097 A	26-03-1998
		EP 0929542 A	21-07-1999
		HR 970474 A	31-12-1998
WO 9809934 A	12-03-1998	AU 4159597 A	26-03-1998
		CA 2256716 A	12-03-1998
		EP 0931045 A	28-07-1999